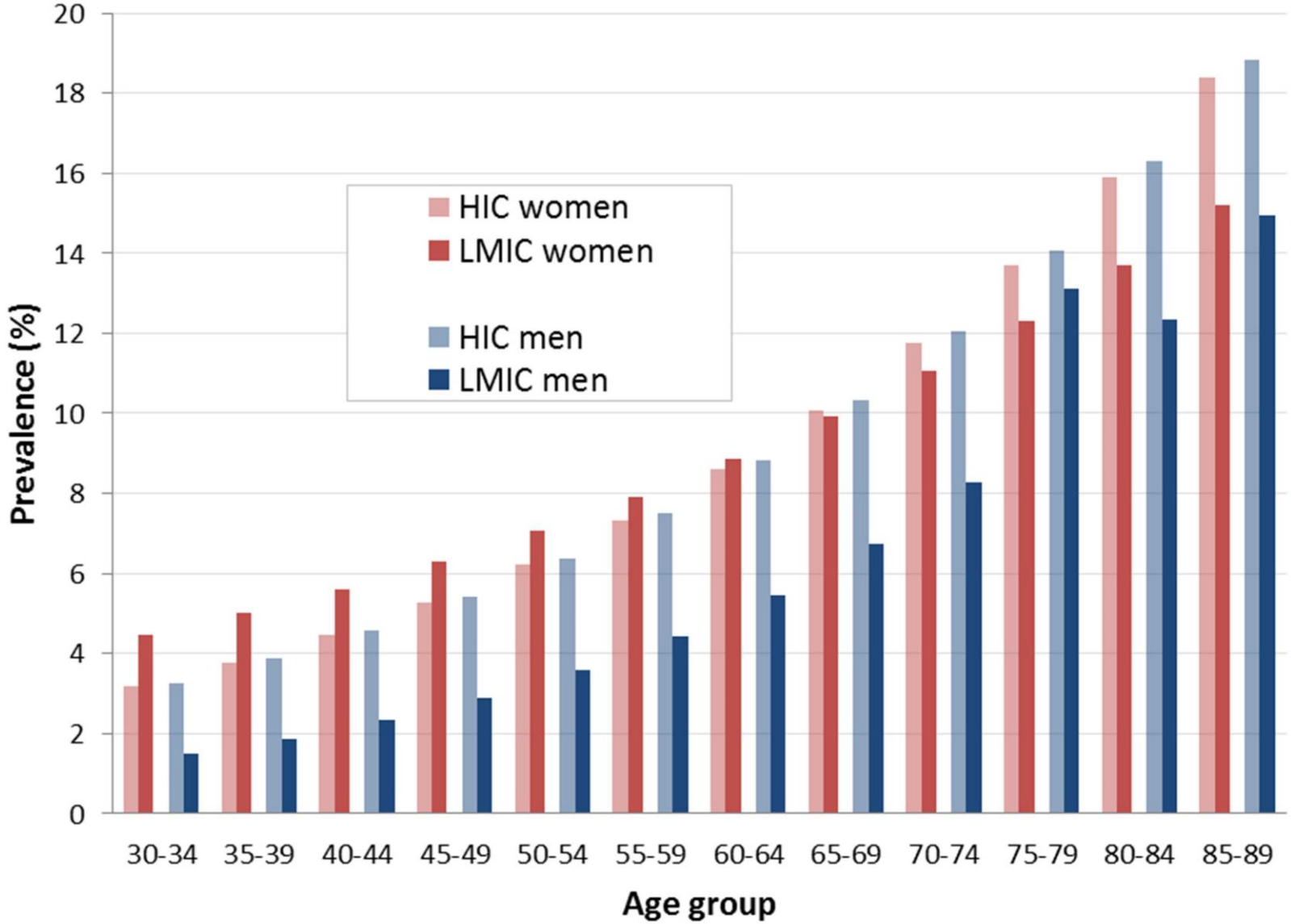
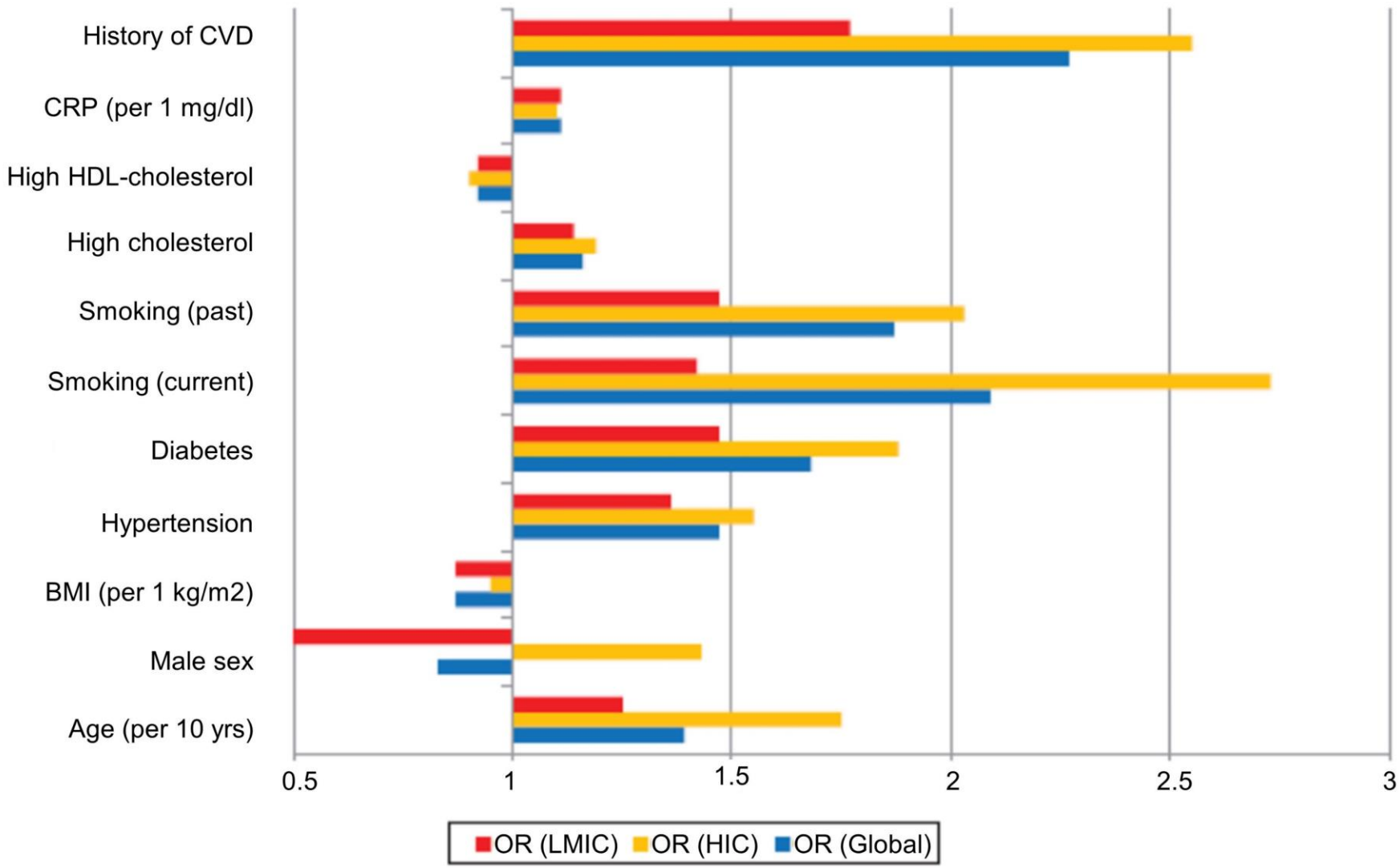
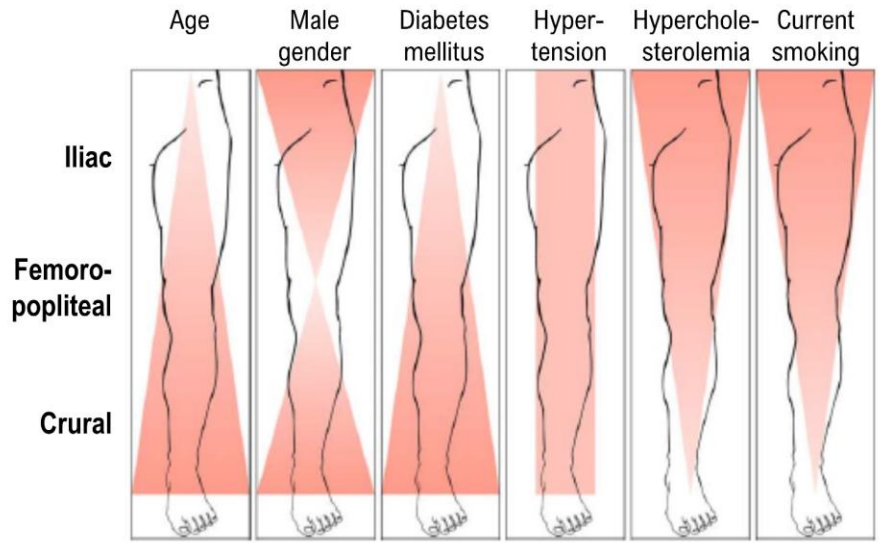
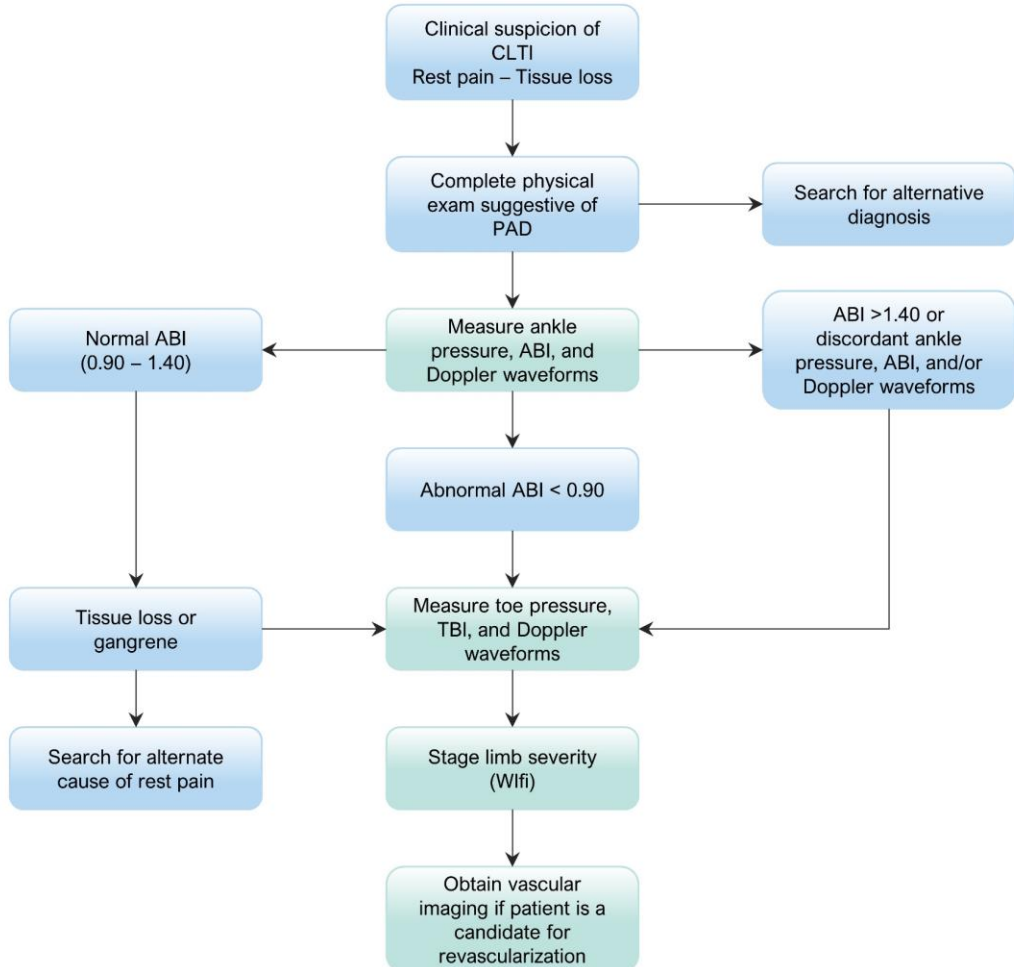

20
18
16
14
12
10
8
6
4
2
0
Prevalence (%)
HIC women
LMIC women
HIC men
LMIC men
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
Age group


History of CVD
CRP (per 1 mg/dl)
High HDL-cholesterol
High cholesterol
Smoking (past)
Smoking (current)
Diabetes
Hypertension
BMI (per 1 kg/m2)
Male sex
Age (per 10 yrs)
0.5
1
1.5
2
2.5
3
OR (LMIC)
OR (HIC)
OR (Global)


Age
Male gender
Diabetes mellitus
Hyper-tension
Hyperchole-sterolemia
Current smoking
Iliac
Femoro-popliteal
Crural


Clinical suspicion of CLTI
Rest pain – Tissue loss
Complete physical exam suggestive of PAD
Search for alternative diagnosis
Normal ABI (0.90 – 1.40)
Measure ankle pressure, ABI, and Doppler waveforms
ABI >1.40 or discordant ankle pressure, ABI, and/or Doppler waveforms
Abnormal ABI < 0.90
Tissue loss or gangrene
Measure toe pressure, TBI, and Doppler waveforms
Search for alternate cause of rest pain
Stage limb severity (WIfi)
Obtain vascular imaging if patient is a candidate for revascularization

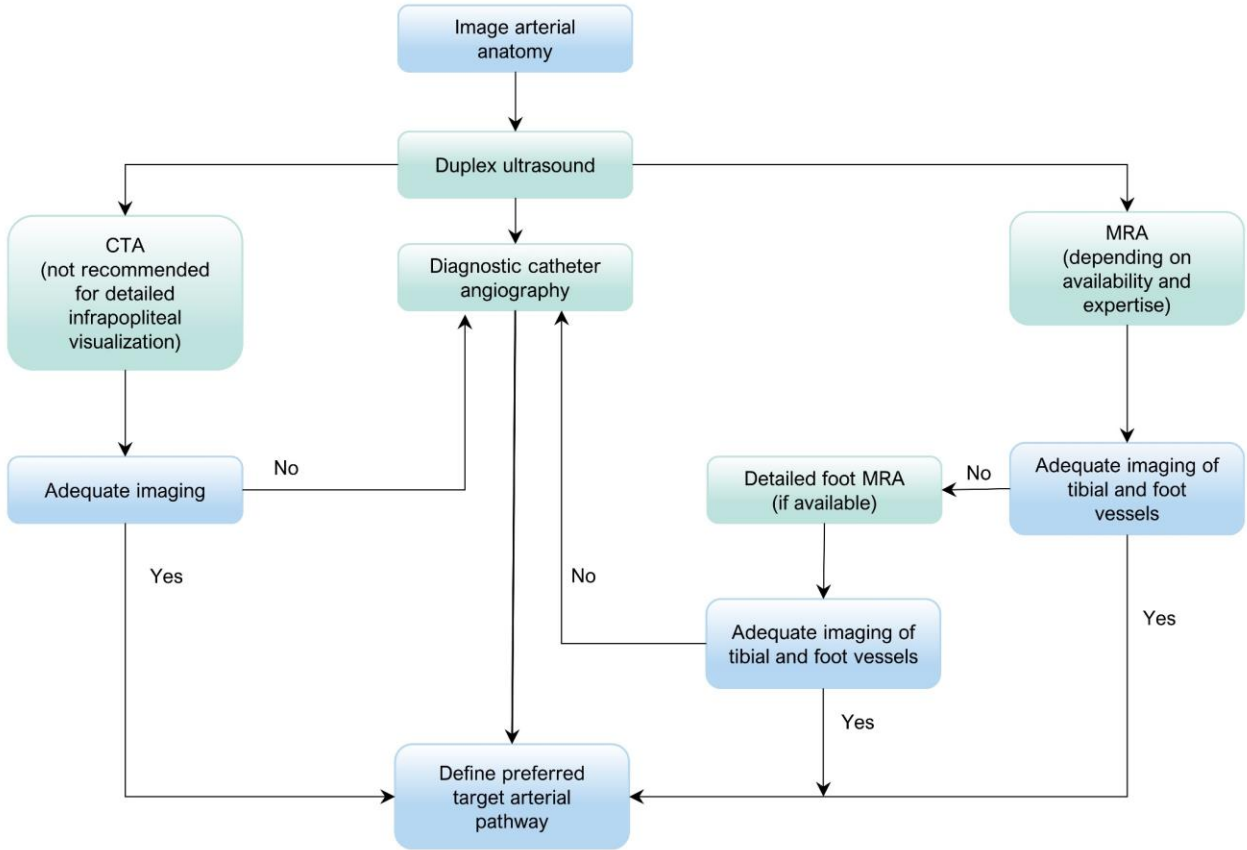
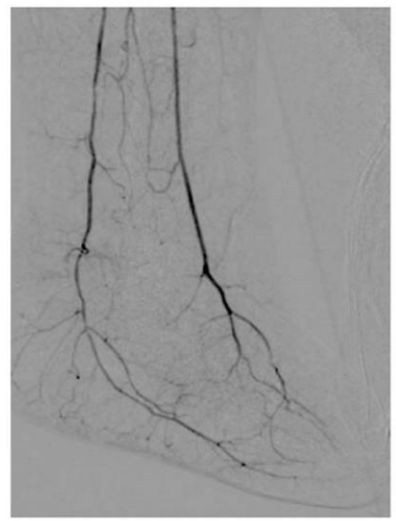
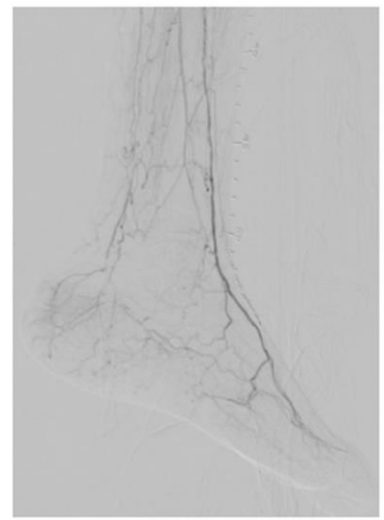


Image arterial anatomy
Duplex ultrasound
CTA (not recommended for detailed infrapopliteal visualization)
Diagnostic catheter angiography
MRA (depending on availability and expertise)
Adequate imaging
No
Yes
Detailed foot MRA (if available)
No
Adequate imaging of tibial and foot vessels
Adequate imaging of tibial and foot vessels
No
Yes
Yes
Define preferred target arterial pathway

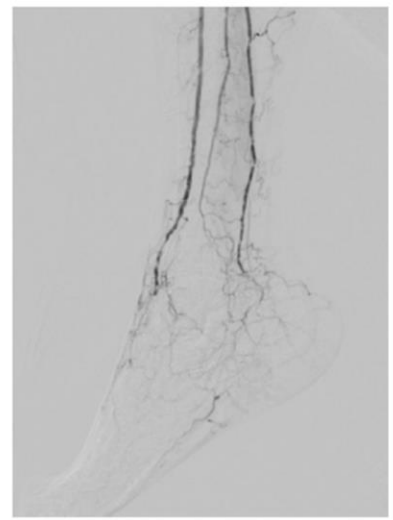
Infra-malleolar/Pedal descriptor	
P0	Target artery crosses ankle into foot, with intact pedal arch
P1	Target artery crosses ankle into foot; absent or severely diseased pedal arch
P2	No target artery crossing ankle into foot



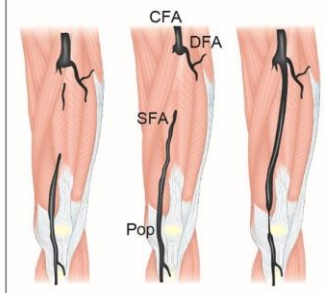
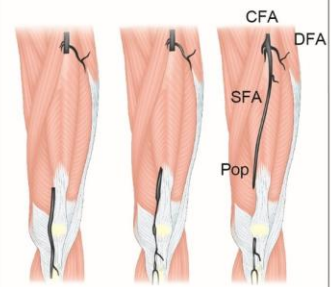
P0

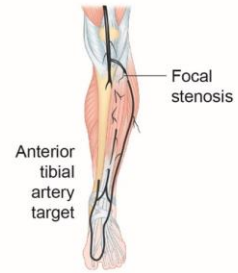
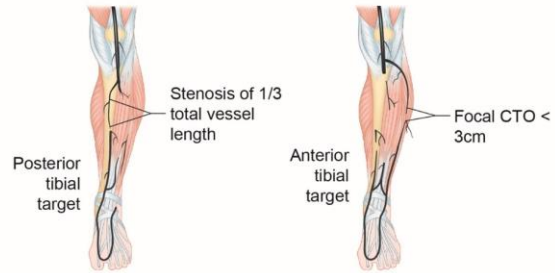
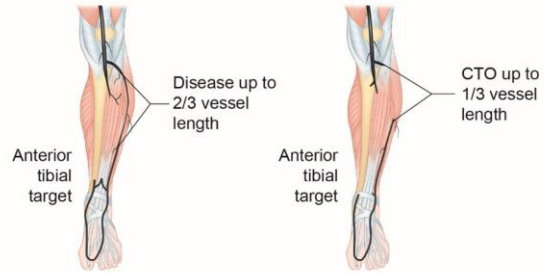
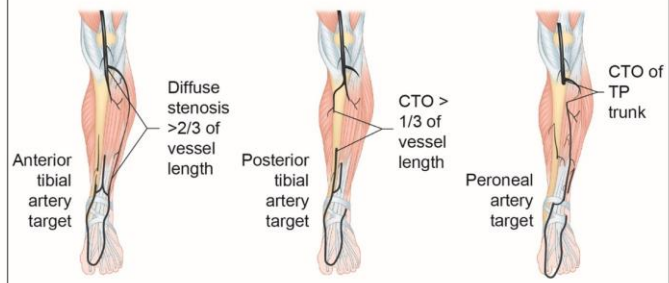


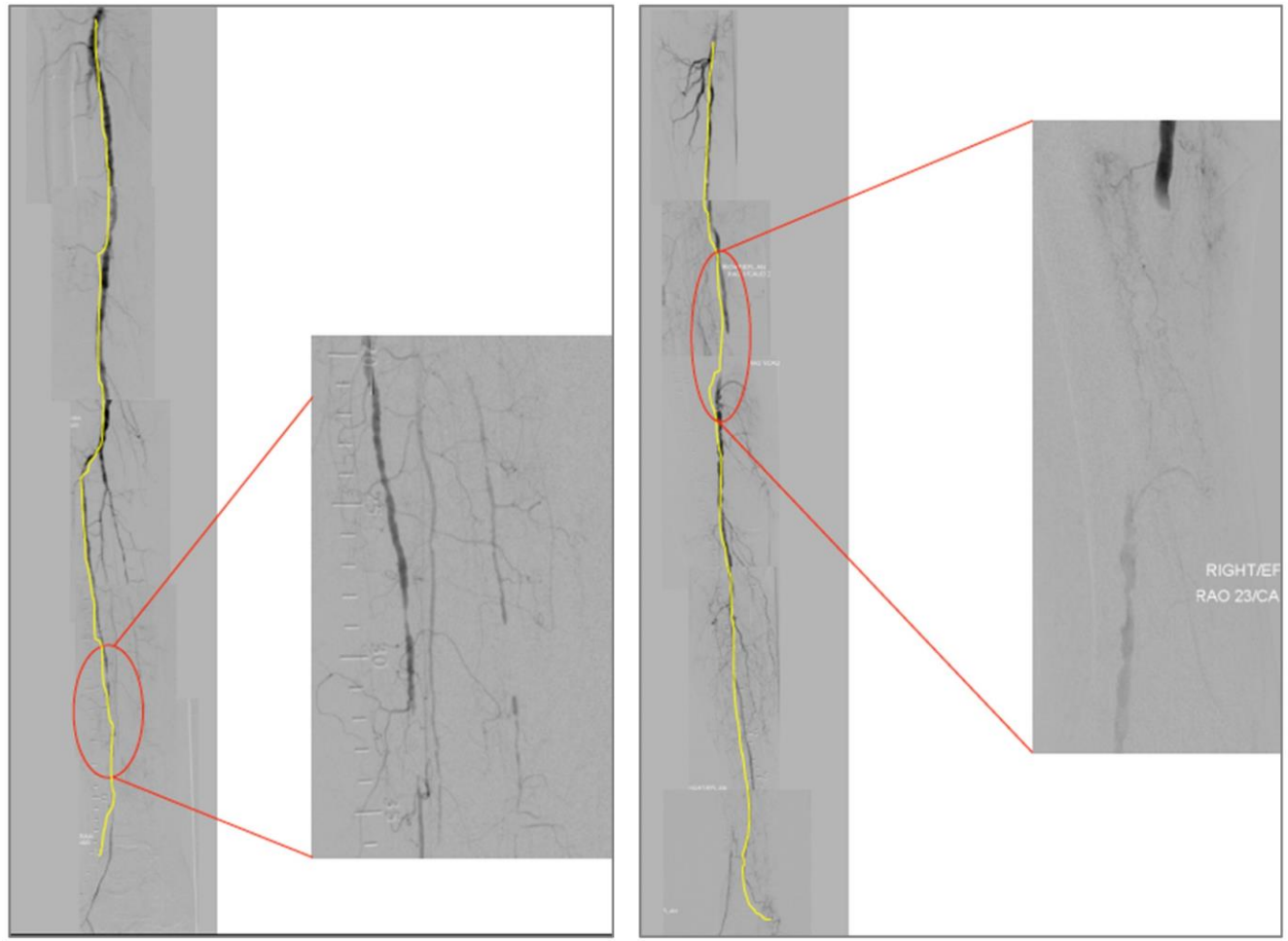
P1

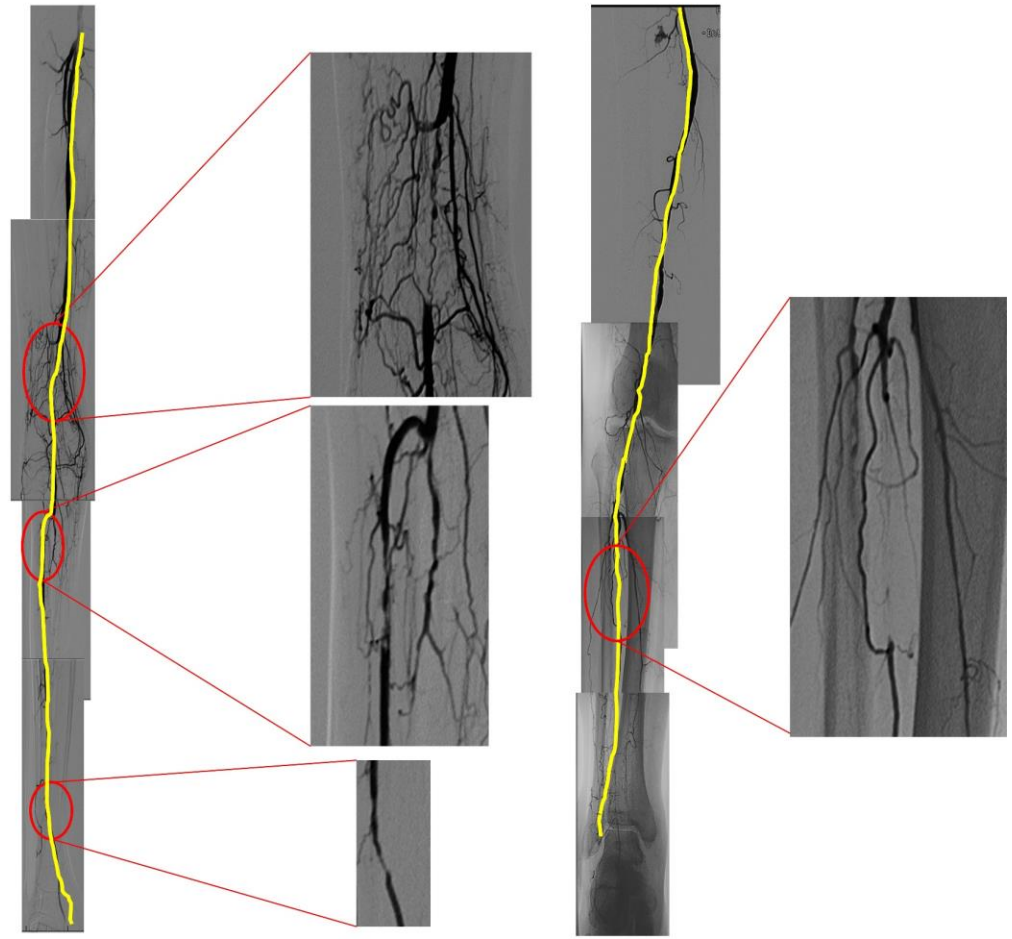


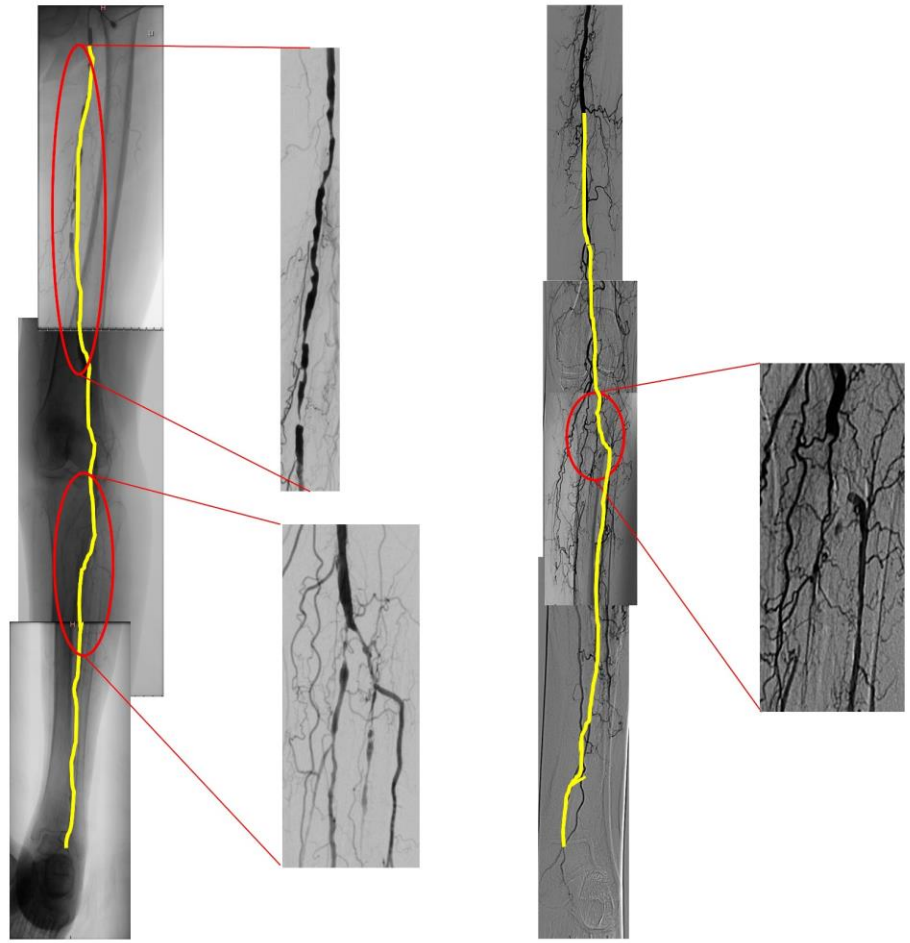
P2

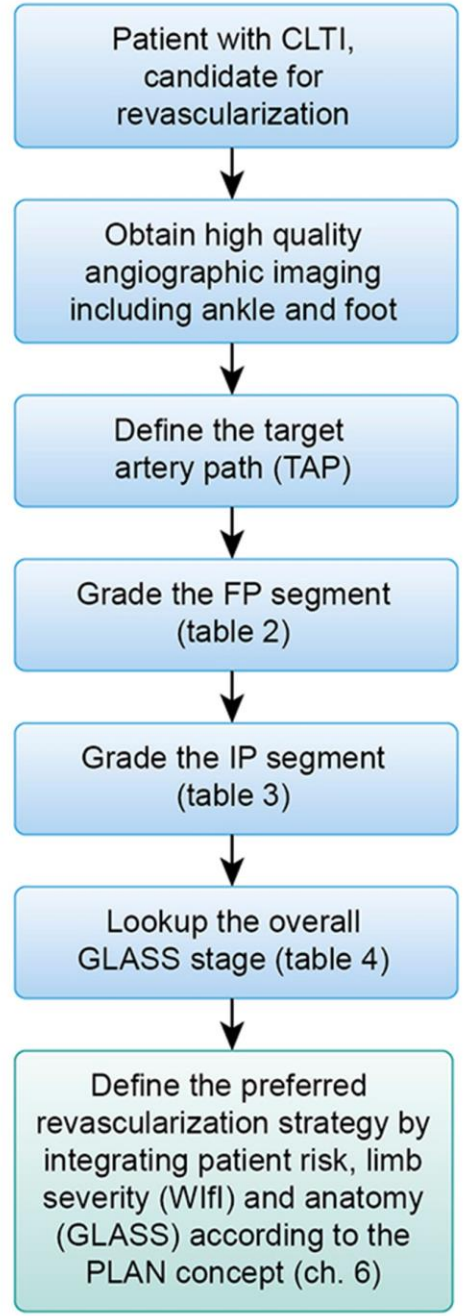
0	Mild or no significant (<50%) disease	
1	• Total length SFA disease <1/3 (<10 cm) • May include single focal CTO (< 5 cm) as long as not flush occlusion • Popliteal artery with mild or no significant disease	
2	• Total length SFA disease 1/3-2/3 (10-20 cm) • May include CTO totaling < 1/3 (10 cm) but not flush occlusion • Focal popliteal artery stenosis <2 cm, not involving trifurcation	
3	• Total length SFA disease >2/3 (>20 cm) length • May include any flush occlusion <20 cm or non-flush CTO 10-20 cm long • Short popliteal stenosis 2-5 cm, not involving trifurcation	
4	• Total length SFA occlusion > 20 cm • Popliteal disease >5 cm or extending into trifurcation • Any popliteal CTO	

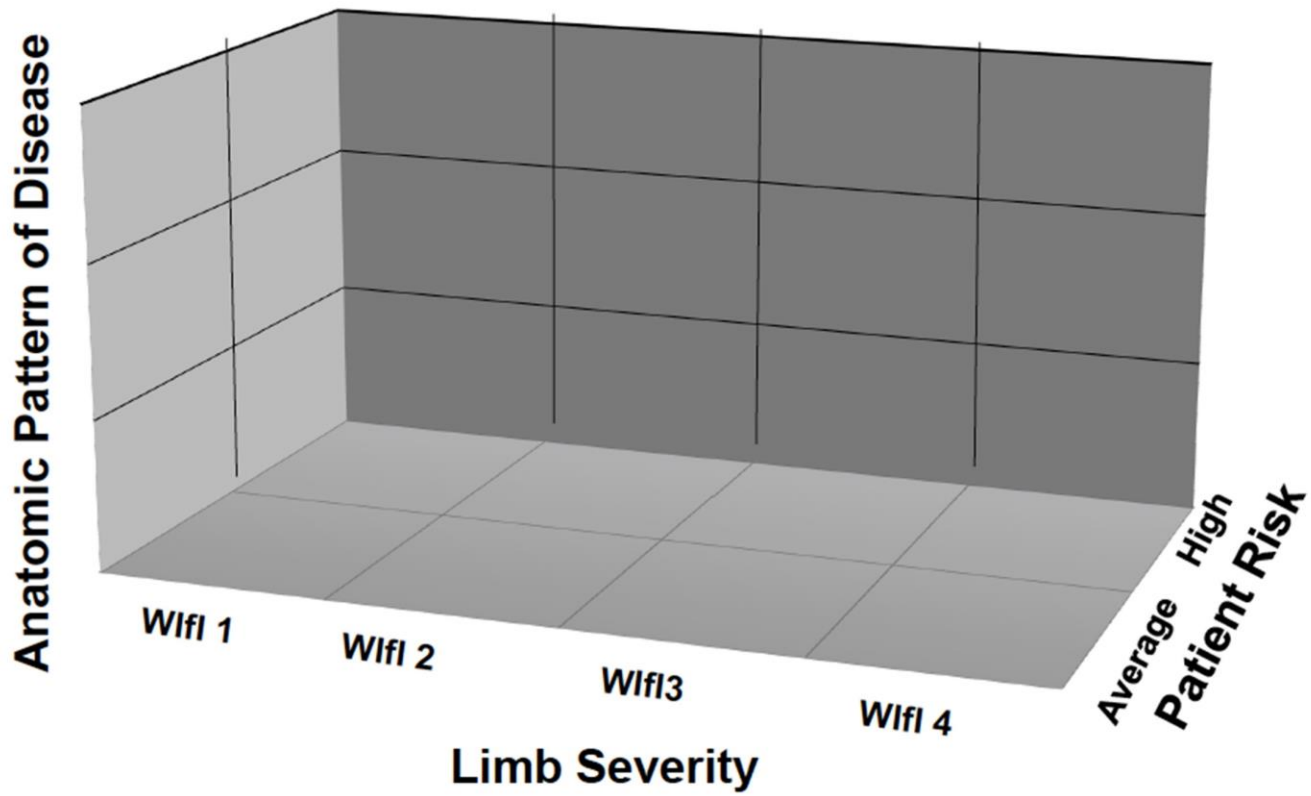
0	• Mild or no significant disease in the primary target artery path	
1	• Focal stenosis of tibial artery < 3cm	
2	• Stenosis involving 1/3 total vessel length • May include focal CTO (<3 cm) • Not including TP trunk or tibial vessel origin	
3	• Disease up to 2/3 vessel length • CTO up to 1/3 length (may include tibial vessel origin but not tibioperoneal trunk)	
4	• Diffuse stenosis > 2/3 total vessel length • CTO > 1/3 vessel length (may include vessel origin) • Any CTO of tibioperoneal trunk if AT is not the target artery	

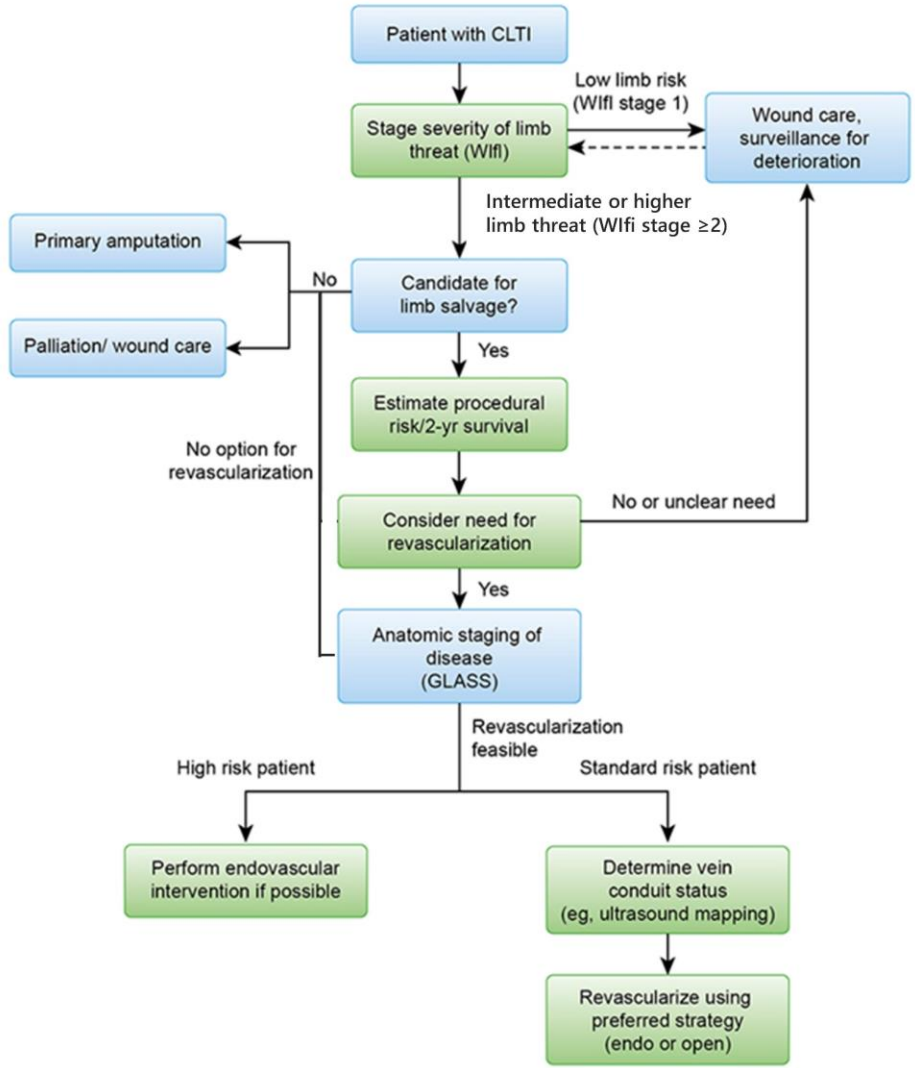

RIGHT/EF
RAO 23/CA

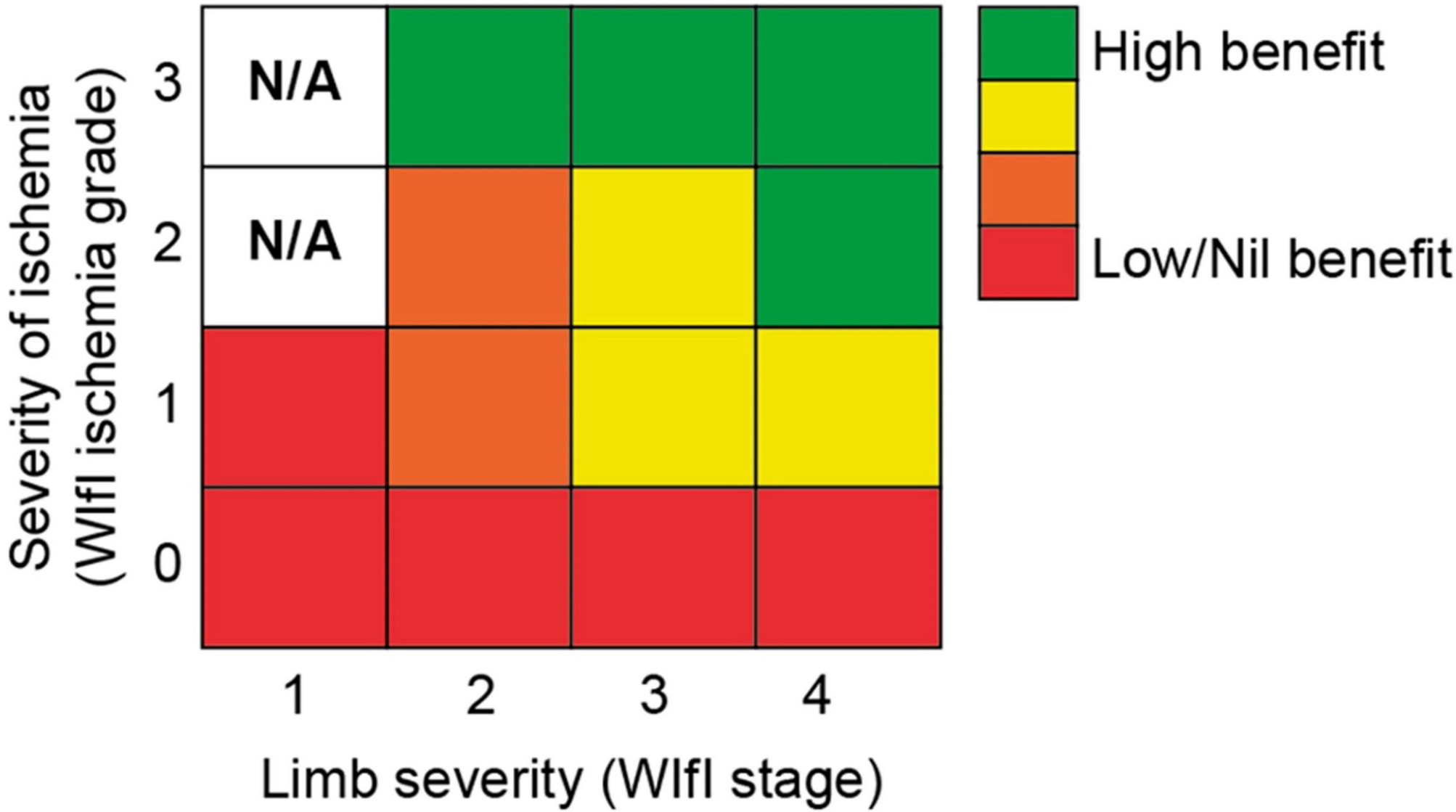


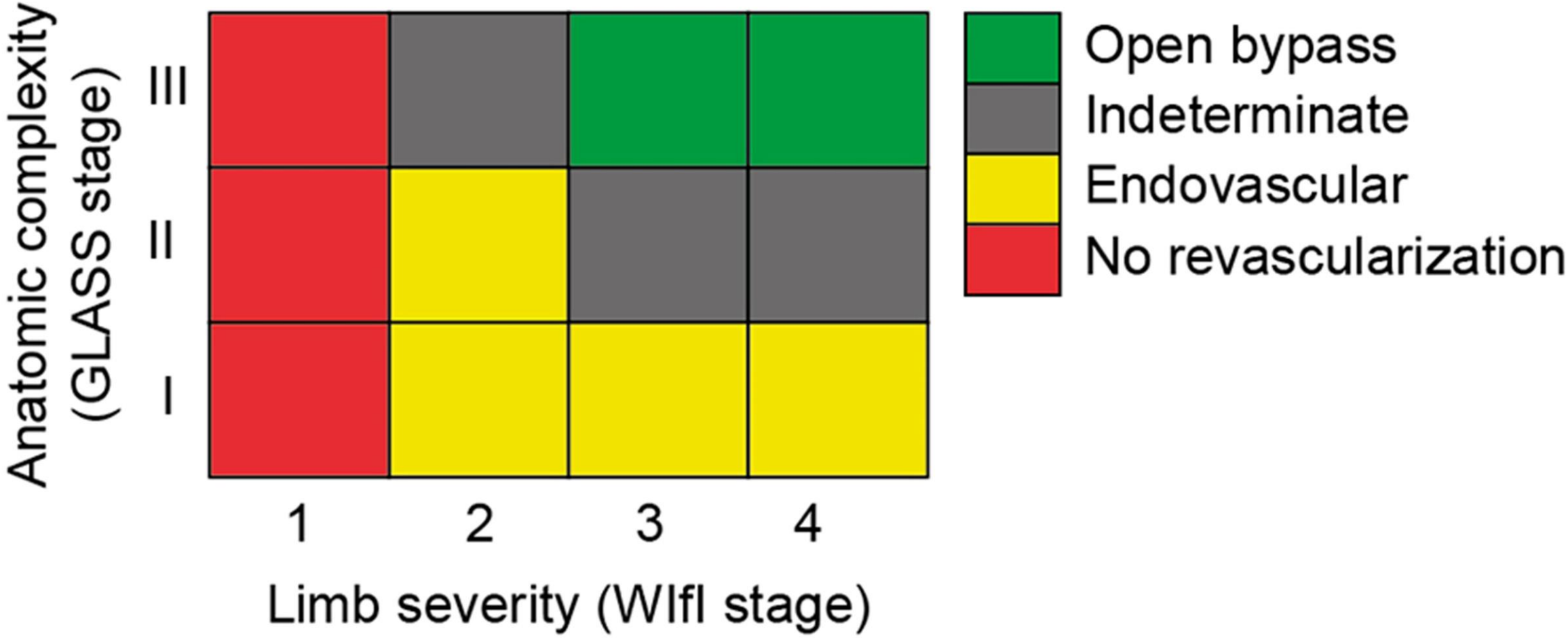


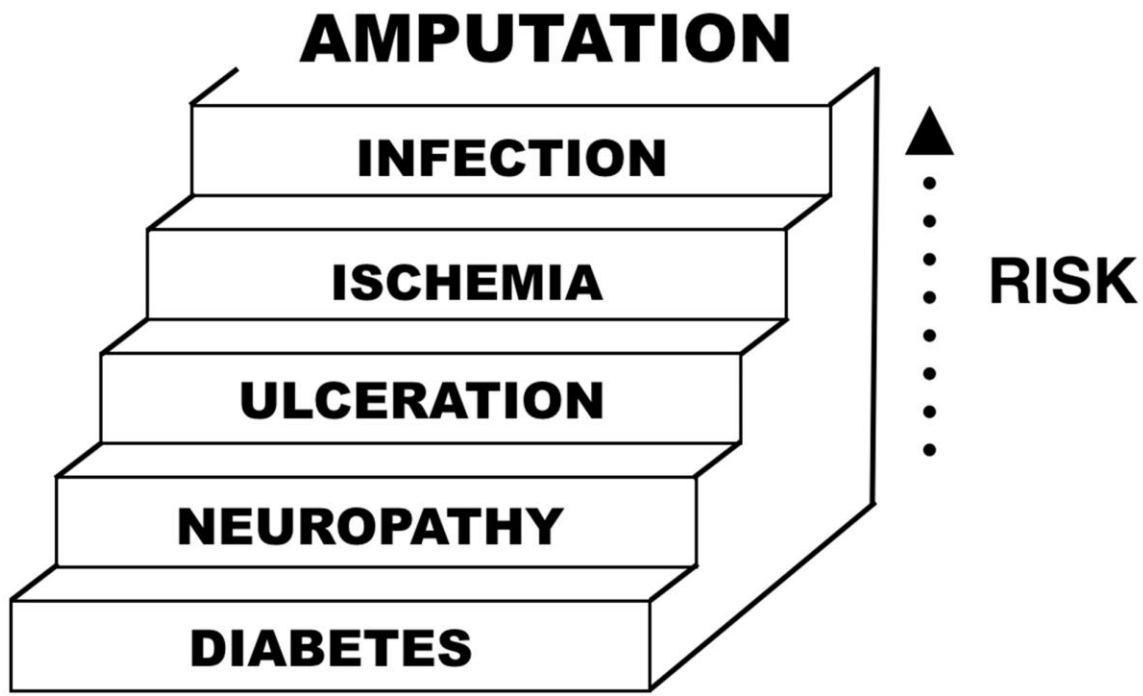

Patient with CLTI, candidate for revascularization
Obtain high quality angiographic imaging including ankle and foot
Define the target artery path (TAP)
Grade the FP segment (table 2)
Grade the IP segment (table 3)
Lookup the overall GLASS stage (table 4)
Define the preferred revascularization strategy by integrating patient risk, limb severity (WIfI) and anatomy (GLASS) according to the PLAN concept (ch. 6)

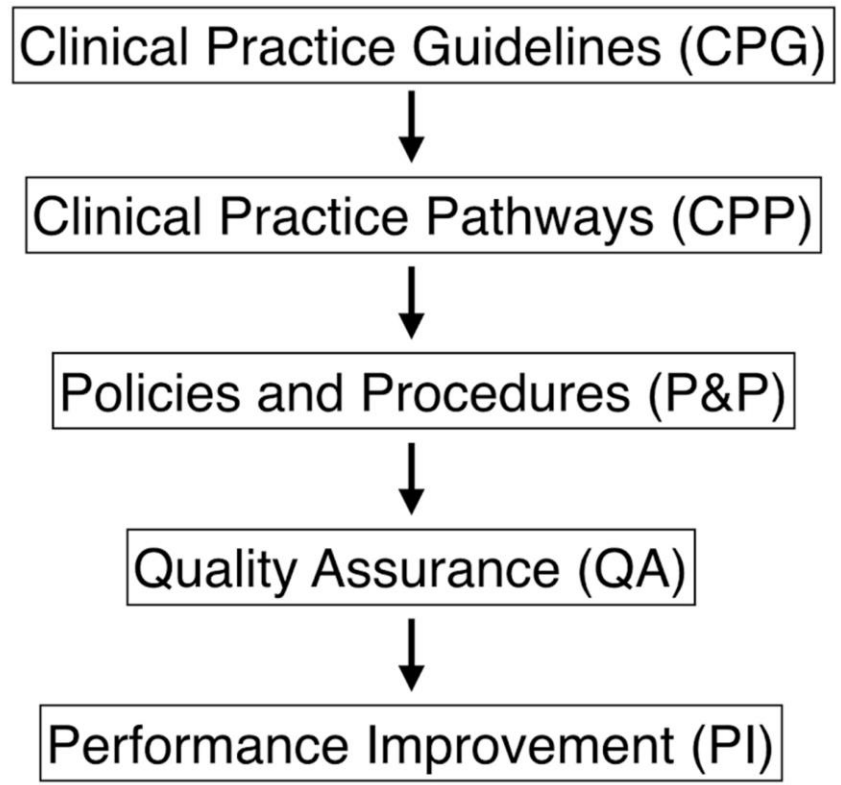

Anatomic Pattern of Disease
WIfI 1
WIfI 2
WIfI3
WIfI 4
Limb Severity
Average
High
Patient Risk


Patient with CLTI
Stage severity of limb threat (WIfI)
Low limb risk (WIfI stage 1)
Wound care, surveillance for deterioration
Intermediate or higher limb threat (WIfi stage ≥2)
Primary amputation
No
Candidate for limb salvage?
Palliation/ wound care
Yes
Estimate procedural risk/2-yr survival
No option for revascularization
Consider need for revascularization
No or unclear need
Yes
Anatomic staging of disease (GLASS)
Revascularization feasible
High risk patient
Standard risk patient
Perform endovascular intervention if possible
Determine vein conduit status (eg, ultrasound mapping)
Revascularize using preferred strategy (endo or open)


Severity of ischemia
(WIfI ischemia grade)
3
2
1
0
N/A
N/A
1
2
3
4
Limb severity (WIfI stage)
High benefit
Low/Nil benefit


Anatomic complexity
(GLASS stage)
III
II
I
1
2
3
4
Limb severity (WIfI stage)
Open bypass
Indeterminate
Endovascular
No revascularization


AMPUTATION
INFECTION
ISCHEMIA
ULCERATION
NEUROPATHY
DIABETES
RISK


Clinical Practice Guidelines (CPG)
Clinical Practice Pathways (CPP)
Policies and Procedures (P&P)
Quality Assurance (QA)
Performance Improvement (PI)

PAD Screening in Diabetic Foot Ulcers

CPG: Society for Vascular Surgery Guidelines*

CPP: Specific pathway adapted to local best practices for vascular disease screening

P&P: All lower extremity ulcers in those with diabetes will undergo screening for peripheral arterial disease by ankle brachial index, toe brachial index, or skin perfusion pressure. Positive tests will be referred to the vascular specialist for evaluation.

QA: 90% of patients with lower extremity ulcers and diabetes will have a screening test

PI: If QA measure is not met, start performance improvement plan:

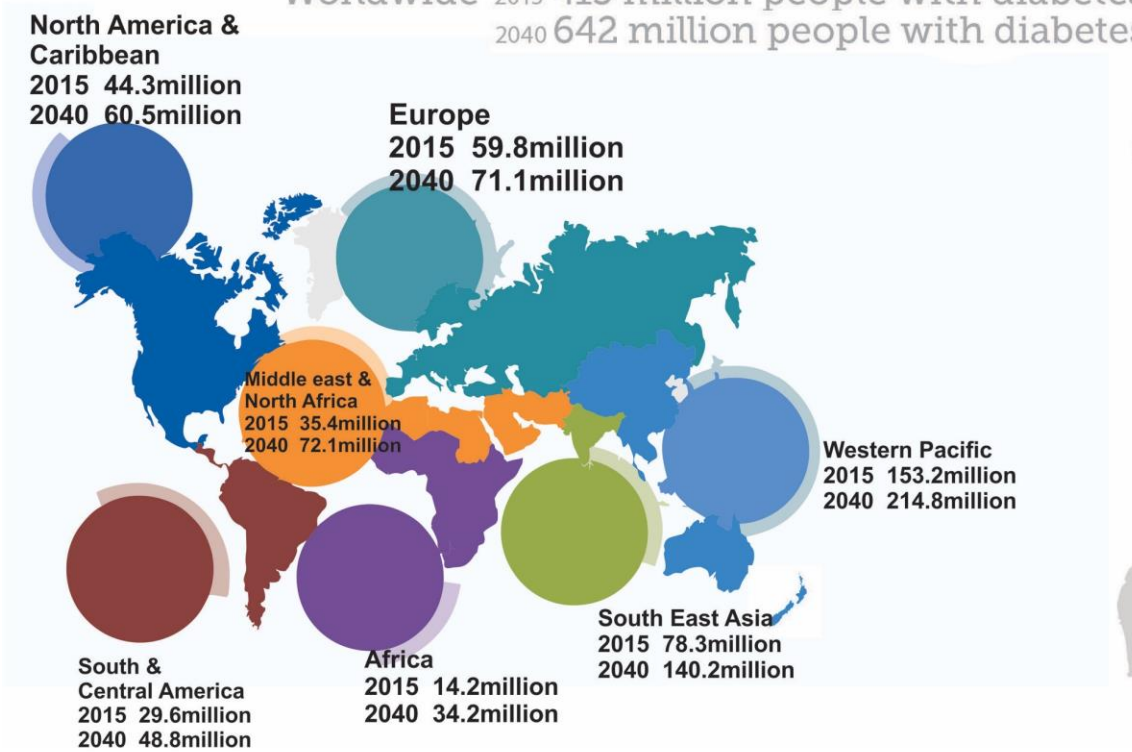
- Assess outcomes to determine impact
- Determine where is the breakdown in compliance
- Reorient staff to the CPP, Policy, and QA expectations
- Retrain staff on peformance and documentation of screening tests
- Reassess compliance in 3 months

International Diabetes Federation

IDF DIABETES ATLAS

2015
Seventh edition

Worldwide 2015 415 million people with diabetes
2040 642 million people with diabetes



2015

One in 11 adults has diabetes

2040

One in 10 adults will have diabetes

One in two adults with diabetes is undiagnosed

Appendix: Summary of Evidence Table

Study	Population	Intervention	Comparison	Methodological Quality	Results
Recommendations 1.1, 1.2					
de Graaff , 2003[1]	Ninety-six patients (128 legs) with clinically suspected critical limb ischemia	clinical judgment and ankle pressure	transcutaneous oxygen pressure and toe blood pressure guided management	Unblinded RCT. The randomization was performed by computer and was prestratified for the presence of diabetes mellitus and bilateral symptoms of CLI	No significant difference in terms of pain score, number of amputations, or death
Wang, 2016[2]	Noninvasive screening tests for the prediction of wound healing and the risk of amputation in diabetic foot ulcers	Various tests	Various tests	A systematic review and meta-analysis of 37 observational studies	For the TcPo2 test, the pooled DOR was 15.81 (95% confidence interval [CI], 3.36-74.45) for wound healing and 4.14 (95% CI, 2.98-5.76) for the risk of amputation. ABI was also predictive but to a lesser degree of the risk of amputations (DOR, 2.89; 95% CI, 1.65-5.05) but not of wound healing (DOR, 1.02; 95% CI, 0.40-2.64). It was not feasible to perform meta-analysis comparing the remaining tests. The overall quality of evidence was limited by the risk of bias and imprecision (wide CIs due to small sample size)
Brownrigg, 2016[3]	prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes	Various tests	Various tests	A systematic review and meta-analysis of 11 observational studies on 9 markers of PAD	Skin perfusion pressure ≥ 40 mmHg, toe pressure ≥ 30 mmHg (and ≥ 45 mmHg) and transcutaneous pressure of oxygen ≥ 25 mmHg were associated with at least a 25% higher chance of healing. Ankle pressure < 70 mmHg and fluorescein toe slope < 18 units each increased the likelihood of major amputation by around 25%.

Study	Population	Intervention	Comparison	Methodological Quality	Results
Beropoulis , 2016[4]	302 Nondiabetic CLI patients treated by endovascular means	The prognostic value of WIfI	None	A retrospective unadjusted analysis was performed of prospectively collected data	The amputation-free survival at 12 months was 87%, 81%, 81%, and 62%, in the very low-risk, low-risk, moderate risk, and very high-risk groups, respectively (P = .106). The difference was statistically significant between the very low-risk and high-risk groups (hazard ratio, 3.4; 95% confidence interval, 1.1-10.3; P = .029)
Ward, 2016[5]	93 Patients who presented to a public hospital with CLI	The prognostic value of WIfI	None	A retrospective adjusted analysis	On multivariable analysis, increasing WIfI amputation score (odds ratio [OR] 1.84, 1.0-3.39) was associated with increased risk of one year major amputation rate
Darling, 2017[6]	596 limbs of patients with a first-time lower extremity revascularization for chronic limb-threatening ischemia	The prognostic value of WIfI	None	A retrospective adjusted analysis	WIfI mean score was predictive in the entire cohort (HR, 1.4; 95% CI, 1.1-1.7), the bypass-only cohort (HR, 1.5; 95% CI, 1.1-1.9), and the endovascular-only cohort (HR, 1.4; 95% CI, 1.0-1.8)
Recommendations 3.4, 3.5, 3.6					
Lijmer, 1996[7]	441 Patients with suspected PAD	noninvasive tests for assessing peripheral arterial disease	None	A retrospective adjusted analysis with blinded readers	For assessing peripheral arterial disease (lesions > or = 50%), determining an ABI is justified (ROC area 0.95 +/- 0.02). For disease localized to the aortoiliac segment, performing a single test, the femoral PI, is sufficient (ROC area 0.80 +/- 0.04). For disease including the femoropopliteal and infrapopliteal segments, a combination of tests is necessary
Aboyans, 2008[8]	510 ambulatory patients (37% had diabetes)	noninvasive tests for assessing peripheral arterial disease	None	Cross-sectional study, unblinded assessment, adjusted analysis	A strong association was found between diabetes and high ABI (OR, 16.0; P < .001). When ABI ranges were compared with TBI

Study	Population	Intervention	Comparison	Methodological Quality	Results
					and Pk-PT results, those with ABI < or =0.90 and ABI > or =1.40 presented similar patterns of abnormalities. Pk-PT or TBI, or both, was abnormal in more than 80% of cases in both ABI < or =0.90 and > or =1.40 groups. The ABI vs TBI relationship appeared linear in nondiabetic patients, but had an inverted J-shape in diabetic patients, suggesting high ABI masked leg ischemia.
Saluan, 2018[9]	556 Patients from the Cohorte des Patients ARTériopathes cohort of patients hospitalized for peripheral arterial disease. Patients with CLI were enrolled according to the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II definition and followed up for at least 1 year	Comparison of major amputation rate according to initial ankle pressure (AP), systolic toe pressure (STP), and forefoot transcutaneous oxygen pressure (TcPO2)	3 comparative tests	The cohort selection was considered adequate (consecutive sampling) and low risk for selection bias but outcome assessment was not adjusted or blinded	AP failed to identify 42% of patients with CLI. After 1 year, 27% of medical and 17% of surgical patients had undergone major amputation. The TP <30 mm Hg predicted major amputation in the whole sample and in the medical group (odds ratio [OR] 3.5 [1.7-7.1] and OR 5 [2-12.4], respectively), but AP did not. The TcPO2 <10 mm Hg also predicted major amputation (OR 2.3 [1.5-3.5] and OR 3.8 [2.1-6.8]). The best predictive thresholds to predict major amputation were STP <30 mm Hg and TcPO2 <10 mm Hg. None of these methods performed before surgery was able to predict outcome in the revascularized patients
Recommendations 3.7, 3.8					
Larch, 1997[10]	Fifty patients with femoropopliteal obstruction were examined immediately before planned	color duplex sonography	digital subtraction	Consecutive sample, 2 readers, cross sectional design	The sensitivity of CDS for detecting a hemodynamically relevant arterial lesion (stenosis or occlusion) was 100% in the

Study	Population	Intervention	Comparison	Methodological Quality	Results
	percutaneous transluminal angioplasty.		angiography		posterior tibial artery, 78% in the anterior tibial artery, and 92% in the peroneal artery
Visser, 2000[11]	31 diagnostic studies	Gadolinium-enhanced MR Angiography	Color-guided Duplex US	Diagnostic meta-analysis, medium risk of bias, adjusted analysis	pooled sensitivity for MR angiography (97.5% [95% CI: 95.7%, 99.3%]) was higher than that for duplex US (87.6% [95% CI: 84.4%, 90.8%]). Pooled specificities were similar: 96.2% (95% CI: 94.4%, 97.9%) for MR angiography and 94.7% (95% CI: 93.2%, 96.2%) for duplex US
Adriaensen, 2004 [12]	73 patients with symptomatic peripheral arterial disease	CT	Digital subtraction angiography	Randomized, unblinded	Further imaging was recommended more often after CT than after DSA (P = .003). Analysis of trends demonstrated increasing confidence in CT and stable confidence in DSA.
Collins, 2007[13]	Symptomatic lower limb peripheral arterial disease	Duplex ultrasound	MR angiography and CT angiography	A systematic review and meta-analysis of 113 observational studies of moderate quality	For the detection of stenosis greater than 50% in the whole leg, MRA (14 studies) had the highest diagnostic accuracy, with sensitivity ranging from 92 to 99.5% and specificity from 64 to 99%. CTA (seven studies) was slightly inferior to MRA, with a sensitivity ranging from 89 to 99% and specificity from 83 to 97%, but better than DUS (28 studies), which had a sensitivity ranging from 80 to 98% and specificity from 89 to 99%
Hingorani, 2004[14]	33 In-patients with chronic lower extremity ischemia	MRA	Contrast arteriography and duplex	Consecutive sample, prospective operative follow up, unblinded	No differences were noted between intraoperative findings and arteriography. Two of the three differences between DA and CA were felt to be clinically significant

Study	Population	Intervention	Comparison	Methodological Quality	Results
			arteriography		whereas 9 of the 12 differences between MRA and CA were felt to be clinically significant. On the basis of these data in this series, MRA does not yet seem to be able to obtain adequate data on infrapopliteal segments, at least not for this highly selected population. When severe tibial calcification or very low flow states are identified, CA may be necessary for patients undergoing DA
Hingorani, 2008[15]	906 patients undergoing lower extremity revascularization	Duplex arteriography (207 intraoperatively, 699 preoperatively)	Contrast arteriography	Consecutive series, comparative, nonrandomized, low risk of bias overall.	Additional CA imaging was required for procedural planning in 102 patients. The areas not visualized well included: iliac (73), femoral (26), popliteal (17), and infrapopliteal (221). Factors associated with increased need to obtain CA included: DM (p<.001), infrapopliteal calcification (p<.001), older age (p = .01) and limb threatening ischemia (p<.001).
Met, 2009[16]	957 patients with intermittent claudication or critical limb ischemia	CTA	digital subtraction angiography	systematic review and meta-analysis of 20 nonrandomized studies of moderate quality	The sensitivity of CTA for detecting more than 50% stenosis or occlusion was 95% (92%-97%) and specificity was 96% (95% CI, 93%-97%). Computed tomography angiography correctly identified occlusions in 94% of segments, the presence of more than 50% stenosis in 87% of segments, and absence of significant stenosis in 96% of segments
Recommendation 4.1					

Study	Population	Intervention	Comparison	Methodological Quality	Results
The Study Group of Critical Chronic Ischemia of the Lower Extremities, 1997[17]	522 patients with chronic critical leg ischemia	Various predictors	None	Prospective observational study with linkage to census information, unblinded	Besides age > or = 70 years (relative risk, RR 1.94; 95% confidence interval (CI) 1.37-2.70), only a history of stroke (RR 1.82; 95% CI 1.19-2.79) and major amputation (RR 1.90; 95% CI 1.30-2.80) were significantly associated with mortality
Recommendation 4.2					
Faglia, 2014[18]	553 diabetic patients admitted because of CLI	Various predictors, ACE and statin	None	Prospective observational study, consecutive sample	Multivariate analysis confirmed the independent role of age, history of stroke, renal insufficiency and dialysis. Combined treatment with ACE and statin appeared to reduce mortality
Armstrong 2014[19]	739 Patients with claudication or critical limb ischemia who underwent diagnostic or interventional lower-extremity angiography	Adhering to all four guideline-recommended therapies (ASA, statins, ACE Inh. and smoking cessation)	Less adherence	Propensity weighting, consecutive cohort, and outcome adjustment. Low risk of bias.	After adjustment for baseline covariates, patients adhering to all four guideline-recommended therapies had decreased MACE (HR, 0.64; 95% CI, 0.45 to 0.89), MALE (major amputation, thrombolysis, or surgical bypass) (HR, 0.55; 95% CI, 0.37 to 0.83), and mortality (HR, 0.56; 95% CI, 0.38 to 0.82), compared to patients receiving less than four of the recommended therapies
Recommendation 4.3					
Antithrombotic Trialists' Collaboration, 2002[20]	Meta-analysis: 287 studies involving 135 000 patients in comparisons of antiplatelet therapy versus control and 77 000 in comparisons of different antiplatelet regimens	antiplatelet	Control	Meta-analysis of randomized trials of various risk of bias	Allocation to antiplatelet therapy reduced the combined outcome of any serious vascular event by about one quarter; non-fatal myocardial infarction was reduced by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth (with no apparent adverse effect on other deaths).

Study	Population	Intervention	Comparison	Methodological Quality	Results
					Absolute reductions in the risk of having a serious vascular event per 1000 were 36 among patients with previous myocardial infarction; 38 among patients with acute myocardial infarction; 36 among those with previous stroke or transient ischaemic attack; 9 among those with acute stroke; and 22 among other high risk patients
Antithrombotic Trialists' Collaboration, 2009[21]	Meta-analysis of 6 primary prevention trials and 16 secondary prevention trials	Aspirin	No aspirin	Meta-analysis of individual participant data from randomized trials at varying risk of bias	-In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events (0·51% aspirin vs 0·57% control per year, p=0·0001). Aspirin allocation increased major gastrointestinal and extracranial bleeds (0·10% vs 0·07% per year, p<0·0001). -In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6·7% vs 8·2% per year, p<0.0001), with a non-significant increase in haemorrhagic stroke but reductions of about a fifth in total stroke (2·08% vs 2·54% per year, p=0·002) and in coronary events (4·3% vs 5·3% per year, p<0·0001). -In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events seemed similar for men and women.
Recommendation 4.4					

Study	Population	Intervention	Comparison	Methodological Quality	Results
CAPRIE Steering Committee, 1996[22]	19,185 patients with atherosclerotic vascular disease manifested as either recent ischemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease	clopidogrel (75 mg once daily)	Aspirin (325 mg once daily)	randomized, blinded, international trial at low risk of bias	Patients treated with clopidogrel had an annual 5.32% risk of ischaemic stroke, myocardial infarction, or vascular death compared with 5.83% with aspirin
Hiatt, 2017[23]	13,885 patients with symptomatic peripheral artery disease, with an ankle-brachial index (ABI) of 0.80 or less or prior revascularization of the lower limbs	ticagrelor (90 mg twice daily)	clopidogrel (75 mg once daily)	Double-blinded randomized trial at low risk of bias	Patients in both groups had similar rates of reduction in cardiovascular events (CV death, myocardial infarction, ischemic stroke) and rates of major bleeding. CV events occurred in 740 of 6955 (10.6%) patients receiving clopidogrel (hazard ratio, 1.02; 95% confidence interval [CI], 0.92 to 1.13; P=0.65), acute limb ischemia occurred in 1.7% of the patients (hazard ratio, 1.03; 95% CI, 0.79 to 1.33; P=0.85) and major bleeding in 1.6% (hazard ratio, 1.10; 95% CI, 0.84 to 1.43; P=0.49).
Recommendation 4.5					
Anand 2017[24]	7470 Patients with peripheral artery disease of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease), of the carotid arteries (previous carotid artery revascularisation or asymptomatic carotid	Oral rivaroxaban (2·5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day (5 mg with aspirin placebo once a day), or to aspirin once a day (100 mg and rivaroxaban placebo twice a day)	3 arms	Multicenter, blinded patients and investigators, RCT at low risk of bias	Rivaroxaban plus aspirin compared with aspirin alone reduced the composite endpoint of cardiovascular death, myocardial infarction, or stroke (126 [5%] of 2492 vs 174 [7%] of 2504; hazard ratio [HR] 0·72, 95% CI 0·57-0·90, p=0·0047), and major adverse limb events including major amputation (32 [1%] vs 60 [2%]; HR 0·54 95% CI 0·35-0·82, p=0·0037). Rivaroxaban plus aspirin combination increased major bleeding compared with the aspirin

Study	Population	Intervention	Comparison	Methodological Quality	Results
	artery stenosis of at least 50%), or coronary artery disease with an ankle-brachial index of less than 0·90				alone group (77 [3%] of 2492 vs 48 [2%] of 2504; HR 1·61, 95% CI 1·12-2·31, p=0·0089),
Recommendation 4.6					
Anand 2007[25]	2161 patients with PAD	antiplatelet agent + oral anticoagulant agent	antiplatelet therapy alone	RCT	Treating 1000 patients with combination therapy as compared with antiplatelet therapy alone for 3 years would lead to 24 fewer cardiovascular events but 28 more episodes of life-threatening bleeding, a net increase in h
Recommendation 4.7					
Mills 2011[26]	Meta-analysis of 10 RCTs enrolling 41778 patients	High dose statin	Low/medium dose statin	RCTs were at low risk of bias	No difference in mortality or CV mortality. High dose reduced composite endpoints of CV death+nonfatal MI and the composite of fatal and nonfatal stroke
MRC/BHF Heart Protection Study, 2002[27]	20,536 adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabetes	40 mg simvastatin daily	Placebo	Blinded randomized trial	All-cause mortality was significantly reduced (1328 [12.9%] deaths among 10,269 allocated simvastatin versus 1507 [14.7%] among 10,267 allocated placebo; p=0.0003), due to a highly significant 18% proportional reduction in the coronary death rate (587 [5.7%] vs 707 [6.9%]; p=0.0005), a marginally significant reduction in other vascular deaths (194 [1.9%] vs 230 [2.2%]; p=0.07), and a non-significant reduction in non-vascular deaths (547 [5.3%] vs 570 [5.6%]; p=0.4)

Study	Population	Intervention	Comparison	Methodological Quality	Results
Meade, 2002[28]	1568 men (aged 35-92 years) with lower extremity arterial disease	400 mg bezafibrate daily	Placebo	Double blinded randomized trial	Bezafibrate did not reduce the incidence of coronary heart disease and stroke (RR 0.96, 95% CI 0.76 to 1.21). There were 90 and 111 major coronary events in the active and placebo groups respectively (0.81, 0.60 to 1.08), of which 64 and 65 were fatal (0.95, 0.66 to 1.37) and 26 and 46 non-fatal (0.60, 0.36 to 0.99). Beneficial effects on non-fatal events were greatest in men aged <65 years at entry, in whom benefit was also seen for all coronary events (0.38, 0.20 to 0.72). There were no significant effects in older men. There were 60 strokes in those on active treatment and 49 in those on placebo (1.34, 0.80 to 2.01). There were 204 and 195 deaths from all causes in the two groups respectively (1.03, 0.83 to 1.26). Bezafibrate reduced the severity of intermittent claudication for up to three years.
Leng, 2000[29]	7 RCTs (698 patients with lower limb artherosclerosis)	Lipid-lowering therapy		Systematic review of 7 RCTs at low risk of bias	The follow-up period varied from four months to three years. The overall quality of the included trials was high. The trials were heterogeneous in terms of inclusion criteria, type of drugs used and outcomes measured. Lipid-lowering therapy produced a marked but non-significant reduction in mortality (odds ratio 0.21, 95% confidence interval 0. 03 to 1.17), but little change in non-

Study	Population	Intervention	Comparison	Methodological Quality	Results
					fatal events (odds ratio 1.21, 95% confidence interval 0.80 to 1.83). In two trials there was a significant overall reduction in disease progression on angiogram (odds ratio 0.47, 95% confidence interval 0.29 to 0.77). The changes in ankle brachial pressure index and walking distance were inconsistent, although trials showed a general improvement in symptoms that could not be combined in a meta-analysis.
Aung, 2007[30]	18 randomized controlled trials (10,049 patients with PAD)	Lipid-lowering therapy		Systematic review of 18 RCTs	The pooled results from all eligible trials indicated that lipid-lowering therapy had no statistically significant effect on overall mortality (Odds Ratio (OR) 0.86; 95% Confidence Interval (CI) 0.49 to 1.50) or on total cardiovascular events (OR 0.8; 95% CI 0.59 to 1.09). However, subgroup analysis which excluded PQRST showed that lipid-lowering therapy significantly reduced the risk of total cardiovascular events (OR 0.74; CI 0.55 to 0.98). This was primarily due to a positive effect on total coronary events (OR 0.76; 95% CI 0.67 to 0.87). Greatest evidence of effectiveness came from the use of simvastatin in people with a blood cholesterol >/= 3.5 mmol/litre (HPS). Pooling of the results from several small trials on a range of different lipid-lowering agents indicated an

Study	Population	Intervention	Comparison	Methodological Quality	Results
					improvement in total walking distance (Weighted Mean Difference (WMD) 152 m; 95% CI 32.11 to 271.88) and pain-free walking distance (WMD 89.76 m; 95% CI 30.05 to 149.47) but no significant impact on ankle brachial index (WMD 0.04; 95% CI -0.01 to 0.09).
Rodriguez, 2017[31]	509,766 patients (aged 21 to 84) in the Veterans Affairs health care system with 2 or more visits for atherosclerotic cardiovascular disease in prior 2 years	high-intensity statin therapy (n=150,928); or low-intensity statin therapy (n=33,920)	No statin (n=92,625)	Retrospective cohort	During a mean follow-up of 492 days, there was a graded association between intensity of statin therapy and mortality, with 1-year mortality rates of 4.0% (5103 of 126 139) for those receiving high-intensity statin therapy, 4.8% (9703 of 200 709) for those receiving moderate-intensity statin therapy, 5.7% (1632 of 28 765) for those receiving low-intensity statin therapy, and 6.6% (4868 of 73 728) for those receiving no statin (P < .001). After adjusting for the propensity to receive high-intensity statins, the hazard ratio for mortality was 0.91 (95% CI, 0.88-0.93) for those receiving high- vs moderate-intensity statins. The magnitude of benefit of high- vs moderate-intensity statins was similar, for an incident cohort hazard ratio of 0.93 (95% CI, 0.85-1.01). For patients aged 76 to 84 years, the hazard ratio was 0.91 (95% CI, 0.87-0.95). Patients treated with maximal doses of

Study	Population	Intervention	Comparison	Methodological Quality	Results
					high-intensity statins had lower mortality (hazard ratio, 0.90; 95% CI, 0.87-0.94) compared with those receiving submaximal doses.
Recommendation 4.8					
SPRINT, 2015[32]	9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes	systolic blood-pressure target of less than 120 mm Hg	target of less than 140 mm Hg	Randomized trial at low risk of bias	Significantly lower rate of the primary composite (CV) outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003).
Bavry 2010[33]	2699 PAD patients followed for a mean of 2.7 years	BP target	NA		All-cause death, nonfatal myocardial infarction, or nonfatal stroke occurred least frequently among PAD patients treated to an average systolic blood pressure of 135 to 145 mm Hg and an average diastolic blood pressure of 60 to 90 mm Hg. PAD patients displayed a J-shape relationship with systolic blood pressure and the primary outcome, although individuals without PAD did not. PAD patients may require a different target blood pressure than those without PAD.
ACCORD Study Group[34]	4733 participants with type 2 diabetes	Intensive therapy, targeting a systolic pressure of less than 120 mm Hg	Standard therapy, targeting a systolic	Low risk of bias, precise	Targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a

Study	Population	Intervention	Comparison	Methodological Quality	Results
			pressure of less than 140 mm Hg		composite outcome of fatal and nonfatal major cardiovascular events
Moise, 2016[35]	The objective of this study was to project the potential value of adding intensive systolic BP goals in high-risk patients to the JNC7 or JNC8 guidelines in a contemporary population of untreated hypertensive individuals aged 35 to 74 years	NA	NA	Simulation and state-transition (Markov cohort) model of incidence, prevalence, mortality, and costs of CVD	Adding intensive systolic blood pressure goals for high-risk patients prevents an estimated 43,000 and 35,000 annual CVD events incremental to JNC8 and JNC7, respectively. Intensive strategies save costs in men and are cost-effective in women compared with JNC8 alone. At a willingness-to- pay threshold of $50,000 per quality-adjusted life years gained, JNC8+intensive had the highest probability of cost-effectiveness in women (82%), and JNC7+intensive the highest probability of cost-effectiveness in men (100%). Assuming higher drug and monitoring costs, adding intensive goals for high-risk patients remained consistently cost-effective compared in men, but not always in women.
Recommendation 4.9					
Nathan, 2005[36]	1441 patients with type 1 diabetes	Intensive therapy	Conventional therapy	Randomized trial at low risk of bias	Intensive treatment reduced the risk of any cardiovascular disease event by 42 percent (95 percent confidence interval, 9 to 63 percent; P=0.02) and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57 percent (95 percent confidence interval, 12 to 79 percent; P=0.02).

Study	Population	Intervention	Comparison	Methodological Quality	Results
Van Dieren 2014[37]	7768 patients with type 2 DM	Intensive glycemic control	Standard control	Randomized trial at low risk of bias	Feasible intensive control of diabetes. No significant reduction in macrovascular disease but a trend toward fewer myocardial infarctions with more intensive glucose control.
Selvin, 2004[38]	13 observational studies (1,699 patients with type 1 diabetes, and 7,435 patients with type 2 diabetes)	NA	NA	Meta-analysis of 13 prospective cohort studies	The pooled relative risk for cardiovascular disease was 1.18; this represented a 1-percentage point increase in glycosylated hemoglobin level (95% CI, 1.10 to 1.26) in persons with type 2 diabetes. Results in persons with type 1 diabetes were similar but had a wider CI (pooled relative risk, 1.15 [CI, 0.92 to 1.43]).
Recommendation 4.10					
Palmer, 2016[39]	301 clinical trials (1 417 367 patient-months)	Glucose-lowering drugs	Other glucose-lowering drugs	Meta-analysis of trials at overall low risk of bias	Compared with metformin, sulfonylurea (standardized mean difference [SMD], 0.18 [95% CI, 0.01 to 0.34]), thiazolidinedione (SMD, 0.16 [95% CI, 0.00 to 0.31]), DPP-4 inhibitor (SMD, 0.33 [95% CI, 0.13 to 0.52]), and α-glucosidase inhibitor (SMD, 0.35 [95% CI, 0.12 to 0.58]) monotherapy were associated with higher HbA1C levels. Sulfonylurea (odds ratio [OR], 3.13 [95% CI, 2.39 to 4.12]; risk difference [RD], 10% [95% CI, 7% to 13%]) and basal insulin (OR, 17.9 [95% CI, 1.97 to 162]; RD, 10% [95% CI, 0.08% to 20%]) were associated with greatest odds of hypoglycemia.
Recommendation 4.11					

Study	Population	Intervention	Comparison	Methodological Quality	Results
Nawaz, 1998[40]	33 inpatients receiving metformin	Contrast angiography		Retrospective case series	Twenty-nine patients had a normal serum creatinine prior to the procedure and none had a rise following angiography. Four patients had an abnormal serum creatinine prior to angiography, all four patients showed significant deterioration and all four patients died, two from unrelated causes and two from acute renal failure and acidosis.
Goergen, 2010[41]	Systematic review of 5 clinical practice guidelines on use of contrast medium in patients taking metformin	Contrast angiography	NA	NA	Recommendations were inconsistent regarding need to withhold metformin in patients with normal vs. abnormal renal function. Not all guidelines included a specific time period. A 48 hour withholding period was most common recommendation. Supporting evidence was of low quality, and connection between evidence and recommendations was unclear.
Recommendation 4.12					
Blomster, 2016[42]	20 countries worldwide participating in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation) trial. (6466 never-smokers, 1550 daily smokers and 3124 former smokers)	Smoking	Non-smoking	Prospective observation of a trial, low risk of bias	Daily smoking was associated with increased risk of major CV events and mortality. Men and women had similar hazard ratios for most subcomponents of outcomes
Newhall, 2017[43]	vascular surgery practices	brief smoking cessation intervention	Control sites	Cluster Randomized trial at low risk of bias	Compared to usual care, patients in the intervention group were more likely to express interest in

Study	Population	Intervention	Comparison	Methodological Quality	Results
					quitting, acknowledge their addictive behaviors, and when re-surveyed three months after intervention, had larger declines in nicotine dependence and health effects domains
Athyros, 2013[44]	1,600 patients with established coronary heart disease, mean follow-up 3-years (RCT of statins)	Atorvastatin	No atorvastatin	Low risk, RCT	Similar relative effects of statins in smokers and non smokers (absolute effects are higher in smokers)
Blomster, 2016[42]	11,140 patients with type 2 diabetes aged ≥ 55 years and in cardiovascular risk at the time of randomisation.	NA	NA	Low risk, Cohort	Daily smoking was associated with increased risk of all primary and secondary outcomes with the exception of major cerebrovascular disease.
Degenais, 2005[45]	8,905 men and women in the Heart Outcomes Prevention Evaluation (HOPE) trial, with either cardiovascular disease, or diabetes with at least one additional risk factor (2728 never smokers, 5241 former smokers, 936 current smokers)	NA	NA	Observational cohort	Patients were followed for 4.5-years. Smokers, as compared with never smokers had adjusted relative risks for cardiovascular death of 1.65 [95% confidence interval (CI), 1.28-2.14], for myocardial infarction of 1.26 (95% CI, 1.01-1.58), for stroke of 1.42 (95% CI, 1.00-2.04), and for total mortality of 1.99 (95% CI, 1.63-2.44).
Recommendation 4.13					
Kondo, 2011[46]	25,464 healthy Japanese men, with no known diseases and not taking medications for hypertension, diabetes or dyslipidemia	NA	NA	Observational cohort	Fewer total CVD events were observed with an increasing duration of quitting, with a statistically significant reduction in mortality with quitting for ≥4 years.
Newhall, 2017[43]	156 smokers at 8 vascular surgery clinics	Surgeon-delivered intervention protocol: cessation counseling,	Usual smoking cessation care	Cluster randomized trial without baseline assessment	More patients in the intervention group reported “a lot” or “some” interest in quitting following their initial appointment with the

Study	Population	Intervention	Comparison	Methodological Quality	Results
		medications and referral to quit line			vascular surgeon (95.4 vs 85.7%, p=0.05). At 3-month follow-up, 37% of those with a strong desire to quit were successful, as compared with 23% of those with a weak desire.
Recommendations 6.3, 6.4, 6.5					
Schanzer, 2008[47]	Patients who underwent infrainguinal vein bypass surgery for CLI. Two datasets were used: the PREVENT III randomized trial (n = 1404) and a multicenter registry (n = 716)	infrainguinal vein bypass surgery	none	Retrospective analysis of prospectively collected data. For a given risk category, the AFS estimate was consistent between the derivation and validation sets	Stratification of the patients in 3 risk categories yielded three significantly different Kaplan-Meier estimates for 1-year AFS (86%, 73%, and 45% for low, medium, and high risk groups, respectively)
Bradbury, 2010[48]	2020 Patients with severe lower limb ischemia due to infrainguinal disease who survived for 2 years after intervention (BASIL trial)	bypass surgery first	balloon angioplasty first	Multivariate Cox model based on RCT at low risk of bias evaluating the effect of baseline variables	Baseline factors that were significant were BASIL randomization stratification group, below knee Bollinger angiogram score, body mass index, age, diabetes, creatinine level, and smoking status. The factors that contributed to the Weibull predictive model were age, presence of tissue loss, serum creatinine, number of ankle pressure measurements detectable, maximum ankle pressure measured, a history of myocardial infarction or angina, a history of stroke or transient ischemia attack, below knee Bollinger angiogram score, body mass index, and smoking status.
Meltzer, 2013[49]	4985 individuals after bypass surgery for CLI from	bypass surgery	None	Retrospective data analysis from a	Higher model scores were significantly associated with higher

Study	Population	Intervention	Comparison	Methodological Quality	Results
	the National Surgical Quality Improvement Program			registry with adequate outcome and exposure ascertainment. Derivatization and validation cohorts.	rates of mortality, all major morbidities, and 30-day major morbidity and mortality
Simons, 2016[50]	7754 Patients with CLI from the national Society for Vascular Surgery Vascular Quality Initiative database	bypass surgery	None	Retrospective data analysis from a registry with adequate outcome and exposure ascertainment.	Three prediction models had similar discriminative performance: (BASIL), Finland National Vascular (FINNVASC) registry, and the modified Project of Ex-vivo vein graft Engineering via Transfection III (PREVENT III [mPIII]). A novel VQI-derived model had improved discriminative ability with a c-index of 0.71.
Biancari, 2007[51]	3,925 Patients s/p infrainguinal surgical revascularization procedures	infrainguinal surgical revascularization procedures	None	Retrospective data analysis from a registry with adequate outcome and exposure ascertainment. Derivatization and validation cohorts.	In the validation data set, the 30-day postoperative mortality/amputation rates in patients with scores of 0, 1, 2, 3, and 4 were 4.8%, 7.5%, 10.1%, 15.9%, and 22.2%, respectively, ($P < 0.0001$); mortality rates were 0.7%, 2.3%, 4.2%, 5.5%, and 14.8%, respectively, ($P < 0.0001$); and major amputation rates were 4.6%, 5.3%, 6.4%, 11.0%, and 14.0%, respectively ($P = 0.011$).
Recommendation 6.10					
Lavery 2008[52]	162 Patients with large, chronic, nonischemic diabetic foot wounds following partial foot amputation.	NA	NA	Re-analysis of RCT, moderate risk of bias	Early changes in percentage of wound area reduction were predictive of final healing at 16 weeks
Sheehan 2003[53]	203 patients with diabetic foot ulcers	NA	NA	Re-analysis of RCT, moderate risk of bias	The percent change in foot ulcer area after 4 weeks of observation is

Study	Population	Intervention	Comparison	Methodological Quality	Results
					a robust predictor of healing at 12 weeks
Snyder, 2010[54]	250 control group subjects from two RCTs of human fibroblast-derived dermal substitute for treating diabetic foot ulcers	NA	NA	Re-analysis of data from two RCTs	Regardless of baseline size category, DFUs with < 50% persistent area of reduction (PAR) at 4 weeks were less likely to heal by 12 weeks than DFUs with > or = 50% PAR (P < or = 0.001). Sensitivity and specificity was higher with cutoff of 4 weeks, than weeks 1 to 3.
Cardinal, 2008[55]	241 diabetic foot ulcers from patients enrolled in RCTs on topic wound treatments	NA	NA	Re-analysis of data from two RCTs	Wound margin advance, initial healing rate, percent wound surface area reduction, and wound healing trajectories (all p<0.001) were powerful predictors of complete wound healing at 12 weeks. Wounds with poor healing progress by these criteria at 4 weeks were highly likely to remain unhealed after 8 additional weeks of treatment.
Recommendation 6.11					
Abu Dabrh, 2015[56]	13 studies enrolling 1527 patients with CLI	Natural history	None	Meta-analysis of observational studies at increased risk of bias	During a median follow-up of 12 months, all-cause mortality rate was 22% (confidence interval [CI], 12%-33%) and major amputation rate was 22% (CI, 2%-42%). Worsened wound or ulcer was found at 35% (CI, 10%-62%). The quality of evidence was low because of increased risk of bias and inconsistency.
Recommendations 6.6, 6.12, 6.13, 6.14					
Cull, 2014[57]	139 patients with foot wounds who presented for	NA	NA	Retrospective analysis of	The WIfI clinical stage was predictive of 1-year limb amputation (stage 1, 3%; stage 2,

Study	Population	Intervention	Comparison	Methodological Quality	Results
	lower extremity revascularization			prospectively collected data.	10%; stage 3, 23%; stage 4, 40%) and wound nonhealing (stage 1, 8%; stage 2, 10%; stage 3, 23%; stage 4, 40%)
Zhan, 2015[58]	201 Patients with threatened limbs	Amputation	Limb salvage	Retrospective cohort, consecutive sample, unadjusted analysis, no blinded outcome adjudication	The amputation group had a significantly higher prevalence of advanced stage 4 patients (P < .001), whereas the limb salvage group presented predominantly as stages 1 to 3. Patients in clinical stages 3 and 4 had a significantly higher incidence of amputation (P < .001), decreased AFS (P < .001), and delayed wound healing time (P < .002) compared with those in stages 1 and 2.
Darling, 2015[59]	596 limbs of patients undergoing an infrapopliteal angioplasty for CLI	Angioplasty	NA	Retrospective cohort identified using administrative codes, consecutive sample, adjusted analysis, no blinded outcome adjudication	One-unit increase in the WIfI composite score is associated with a decrease in wound healing (HR, 1.2; 95% CI, 1.1-1.4) and an increase in the rate of stenosis (HR, 1.2; 95% CI, 1.1-1.4) and major amputations (HR, 1.4; 95% CI, 1.2-1.8).
Causey, 2016[60]	143 patients hospitalized for threatened limb	NA	NA	retrospective analysis of prospectively gathered registry data of consecutive patients	Increased WIfI stage was associated with major adverse limb events (P = .018), reduced limb salvage (P = .037), and decreased AFS (P = .048). PREVENT III risk score category was associated with mortality (P < .001) and AFS (P < .001).
Robinson, 2017[61]	280 threatened limbs.	NA	NA	retrospective analysis of prospectively gathered registry data of consecutive	Increasing WIfI stage was associated with decreased 1-year Kaplan-Meier limb salvage (stage 1: 96%, stage 2: 84%, stage 3: 90%, and stage 4: 78%; P = .003) and

Study	Population	Intervention	Comparison	Methodological Quality	Results
				patients, adjusted analysis	amputation-free survival (P = .006).
Recommendation 6.17					
Seeger, 1987[62]	51 Patients who had lower extremity revascularization	Real-time imaging of the saphenous and cephalic veins.	Patients who had similar procedures in the 12 months before the use of vein mapping	Pre post nonrandomized study	Preoperative mapping was found to be accurate in 50 to 51 patients (98%). Vein size as determined by B-mode ultrasound correlated well with angiograms, R = 0.85 overall with R greater than 0.9 in the last 7 months of the study. Wound complications occurred in 2% of the patients who had preoperative mapping and in 17% of the historic controls
Wengerter, 1990[63]	239 infrapopliteal reversed greater saphenous vein graft bypasses placed for critical ischemia over a 7-year period	NA	NA	Nonrandomized prospective cohort study, unblinded	A pattern of increasing graft patency and limb salvage was noted as the minimum external diameter increased from less than 3.0 mm to greater than or equal to 4.0 mm
Schanzer, 2007[64]	1404 North American patients with critical limb ischemia	lower extremity bypass	NA	Secondary analysis of RCT	Vein diameter and conduit type were the dominant technical determinants of early and late graft failure.
Recommendations 6.20, 6.21, 6.22, 6.23, 6.24					
Harward, 1995[65]	450 patients undergoing lower extremity arterial reconstruction	NA	NA	Retrospective unblinded cohort study	The majority of complications and deaths occurred in patients undergoing aortic inflow plus complex outflow procedures (profundaplasty and/or composite bypass conduits), in which the morbidity/mortality rates were 84.2% and 47.4%, respectively, compared with rates of 45.7% and 2.9% ($p < 0.01$) after all other inflow/outflow procedures. The increased difficulty of these

Study	Population	Intervention	Comparison	Methodological Quality	Results
					complex procedures is reflected in the significantly greater blood loss and operative times (1853 mL and 10.0 hours) compared with similar values (1125 mL and 7.7 hours)($p < 0.01$) for all other inflow/outflow procedures
Zukauskas, 1995[66]	1953 aortofemoral reconstructions were performed during a 6-year period	NA	NA	Retrospective unblinded cohort study	Single-stage multisegment reconstruction for multilevel arterial occlusive disease is a safe and effective method of treating critical limb ischaemia
Recommendation 6.25					
Jongkind, 2010[67]	Meta-analysis of 19 nonrandomized studies (1711 patients)	Endovascular approach	NA	Uncontrolled studies	Technical success was achieved in 86% to 100% of the patients. Clinical symptoms improved in 83% to 100%. Mortality was described in seven studies and ranged from 1.2% to 6.7%. Complications were reported in 3% to 45% of the patients. Most common complications were distal embolization, access site hematomas, pseudoaneurysms, arterial ruptures, and arterial dissections.
Ye, 2011[68]	Meta-analysis of 16 endovascular treatment studies (958 patients)	Endovascular approach	NA	Retrospective, uncontrolled studies	Technical success was achieved in 92.8% of patients (95% confidence interval [CI], 89.8%-95.0%, 749 cases). Primary patency at 12 months was 88.7% (95% CI, 85.9%-91.0%, 787 cases). Subgroup analyses demonstrated a technical success rate of 93.7% (95% CI, 88.9%-96.5%) and a 12-month primary patency rate of 89.6% (95% CI, 84.8%-93.0%) for

Study	Population	Intervention	Comparison	Methodological Quality	Results
					TASC C lesions. For TASC D lesions, these rates were 90.1% (95% CI, 76.6%-96.2%) and 87.3% (95% CI, 82.5%-90.9%), respectively
Deloose, 2017[69]	120 patients with TASC II A & B iliac lesions	Endovascular treatment		Multicenter prospective cohort	The primary patency rate for the total patient population was 97.4%. The primary patency rates at 12 months for the TASC II class A and TASC II class B(C) lesions were respectively 98.3% and 96.6%.
Recommendation 6.26					
Indes, 2013[70]	Meta-analysis of 29 open bypass studies (3733 patients) and 28 endovascular treatment studies (1625 patients) in aortoiliac occlusive disease	direct open bypass	Endovascular treatment	Mostly observational comparative studies	Mean length of hospital stay (LOS) was 13 days for open bypass vs. 4 days for endovascular treatment procedures (p<0.001). The open bypass group experienced more complications (18.0% vs. 13.4%, p<0.001) and greater 30-day mortality (2.6% vs. 0.7%, p<0.001). At 1, 3, and 5 years, pooled primary patency rates were greater in the open bypass group vs. the endovascular cohort (94.8% vs. 86.0%, 86.0% vs. 80.0%, 82.7% vs. 71.4%, respectively; all p<0.001); the same was true for secondary patency [95.7% vs. 90.0% (p=0.002), 91.5 vs. 86.5% (p<0.001), and 91.0% vs. 82.5% (p<0.001), respectively]
Chiu, 2010[71]	29 bypass studies	Bypass	Endovascular treatment	Systematic review of mostly observational studies	Operative mortality rate was 4.1% for aortofemoral bypass (AFB), 2.7% for iliofemoral bypass (IFB), and 2.7% for aortoiliac endarterectomy (AIE). Systematic morbidity rate was 16%, 18.9%, and 12.5%. Local morbidity rate

Study	Population	Intervention	Comparison	Methodological Quality	Results
					was 6.3% for AFB, 5.7% for IFB, and 2.4% for AIE. Graft-related morbidity/intervention failure rates were 3.1%, 4.2%, and 3.8%. 8 studies reported infection rates following AFB, with a combined rate of 0.4%. 5-year patency rates for patients with CLI were 79.8% for AFB and 74.1% for IFB, and 81.7% for AIE.
Ricco, 2008[72]	143 patients with unilateral iliac artery occlusive disease and disabling claudication	Crossover bypass	Direct bypass		Primary patency at 5 years was higher in the direct bypass group than in the crossover bypass group (92.7 +/- 6.1% vs 73.2 +/- 10%, P = .001). Assisted primary patency and secondary patency at 5 years were also higher after direct bypass than crossover bypass (92.7 +/- 6.1% vs 84.3 +/- 8.5%, P = .04 and 97.0 +/- 3.0% vs 89.8 +/- 7.1%, P = .03, respectively). Patency at 5 years after crossover bypass was significantly higher in patients presenting no or low-grade SFA stenosis than in patients presenting high-grade (> or =50%) stenosis or occlusion of the SFA (74.0 +/- 12% vs 62.5 +/- 19%, P = .04). In both treatment groups, patency was comparable using polytetrafluoroethylene (PTFE) and polyester grafts. Overall survival was 59.5 +/- 12% at 10 years.
Recommendation 6.27					

Study	Population	Intervention	Comparison	Methodological Quality	Results
Kang, 2008[73]	65 limbs in 58 patients with occlusive disease of the common femoral artery	common femoral endarterectomy	NA	Retrospective, unblinded, adjusted analysis	Technical success was achieved in 100% of the cases. 1- and 5-year primary patencies were 93% and 91%, respectively
Ballotta, 2010[74]	117 patients	common femoral endarterectomy	NA	Retrospective, unblinded, unadjusted analysis	There were no perioperative deaths or major complications. 7-year rates of freedom from further revascularization and survival were 79% and 80%, respectively.
Recommendation 6.28					
Chang 2008[75]	171 patients (mean age, 67 +/- 10 years; 38% female; 35% diabetic)	CFA endarterectomies and iliac stent/stent grafting	NA	Retrospective, noncomparative, nonblinded	Technical success occurred in 98% of patients. Clinical improvement was seen in 92% of patients. Mean ankle-brachial index increased from 0.38 +/- 0.32 to 0.72 +/- 0.24. Median length of stay was 2 days (range, 1-51 days). Thirty-day mortality was 2.3% and 5-year survival was 60%. Five-year primary, primary-assisted, and secondary patencies were 60%, 97%, and 98% respectively. Endovascular reintervention was required in 14% of patients; inflow surgical procedures were required in 10%. By logistic regression analysis, use of stent grafts compared with bare stents was associated with significantly higher primary patency (87% +/- 5% vs 53% +/- 7%; P < .01).
Recommendation 6.29					
Baumann, 2011[76]	98 patients with symptomatic obstructions of the common femoral artery	endovascular therapy	NA	Consecutive series, adjusted analysis	Primary sustained clinical improvement rates at 3, 6, 12, and 24 months were 55%, 55%, 40%, and 0% in CLI patients and 81%, 75%, 68%, and 52% in claudicants,

Study	Population	Intervention	Comparison	Methodological Quality	Results
					respectively. Limb salvage rates at 24 months were 94% in CLI patients and 100% in claudicants.
Bonvini, 2011[77]	97 patients with symptomatic obstructions of the common femoral artery	endovascular therapy	NA	Prospectively maintained single-center database. Retrospective analysis, unblinded and unadjusted	Failures-defined as a final angiographic result with a >30% residual stenosis-were observed on 26 occasions (7.2%). In-hospital major (i.e., requiring surgery) and minor (i.e., treated percutaneously or conservatively) complications occurred in 5 (1.4%) and 18 (5.0%) procedures, respectively.
Gouëffic, 2017[78]	117 patients with de novo atherosclerotic lesions of the CFA	Stenting	Surgery	Randomized trial, moderate risk of bias	Primary outcome (mortality and complications) occurred in 16 of 61 patients (26%) in the surgery group and 7 of 56 patients (12.5%) in the stenting group (odds ratio: 2.5; 95% confidence interval: 0.9 to 6.6; p = 0.05). The mean duration of hospitalization was significantly lower in the stenting group (3.2 ± 2.9 days vs. 6.3 ± 3 days; p < 0.0001). At 24 months, the sustained clinical improvement, the primary patency rate, and the target lesion and extremity revascularization rates were not different in the 2 groups
Siracuse, 2016[79]	1014 patients with PAD	isolated CFA intervention with or without a DFA intervention	NA	Retrospective unblinded, noncomparative	Survival was 92.9% at 1 year and 87.2% at 3 years. Amputation-free survival, freedom from loss of patency or death, and reintervention-free survival were 93.5%, 83%, and 87.5% at 1 year, respectively. Multivariable predictors of mortality were tissue loss, chronic obstructive

Study	Population	Intervention	Comparison	Methodological Quality	Results
					pulmonary disease, end-stage renal disease, urgent case, and age, whereas aspirin use and non-Caucasian race were protective. Tissue loss, rest pain, COPD, end-stage renal disease, stent use, nonambulatory status, and female sex were predictive of major amputation whereas aspirin use, P2Y12 antagonist use, statin use, and initial technical success were protective
Recommendations 6.32, 6.40, 6.41					
Almasri, 2017[80]	44 studies that enrolled 8,602 patients with chronic limb threatening ischemia	All infrainguinal revascularization procedures	NA	Noncomparative meta-analysis	Prosthetic bypass outcomes were notably inferior to vein bypass in terms of amputation and patency outcomes, especially for below knee targets at two years and beyond. Drug eluting stents demonstrated improved patency over bare metal stents in infra-popliteal arteries (primary patency: 73% vs. 50% at 1 year, and was at least comparable to balloon angioplasty (66% primary patency), albeit within an anatomically restricted cohort of CLTI patients. Survival, major amputation and amputation-free survival at two years were broadly similar between endovascular interventions and vein bypass, with prosthetic bypass having higher rates of limb loss
Recommendations 6.33, 6.34, 6.35, 6.36, 6.37					
See Abu Dabrh, 2015, Zhan 2015, Darling 2015, Causey 2016, Robinson, 2017					
Recommendation 6.38					

Study	Population	Intervention	Comparison	Methodological Quality	Results
Chae, 2016[81]	Meta-analysis of 727 patients with arterial occlusive disease in diabetic feet	angiosome-targeted angioplasty	nonangiosome-targeted angioplasty	4 nonrandomized comparative studies at increased risk of bias	Overall limb salvage and wound healing rates were significantly higher (Odds ratio = 2.209, 3.290, p = 0.001, p<0.001) in patients who received angiosome-targeted angioplasty. The revision rate was not significantly different (Odds ratio = 0.747, p = 0.314)
Jongsma 2017[82]	Meta-analysis of 19 cohort studies with 3932 patients with CLI	Direct revascularization according to the angiosome concept,	indirect revascularization	Nonrandomized studies at low risk of bias	Direct revascularization significantly improved wound healing (risk ratio [RR], 0.60; 95% confidence interval [CI], 0.51-0.71), major amputation (RR, 0.56; 95% CI, 0.47-0.67), and amputation-free survival rates (RR, 0.83; 95% CI, 0.69-1.00)
Biancari, 2014[83]	Systematic review and meta-analysis of 9 cohort studies (1290 legs)	Direct revascularization according to the angiosome concept,	indirect revascularization	Retrospective studies at increased risk of bias	The risk of unhealed wound was significantly lower after direct revascularization (HR 0.64, 95% CI: 0.52-0.8, I2 0%, four studies included) compared with indirect revascularization. Direct revascularization was also associated with significantly lower risk of major amputation (HR 0.44, 95% CI: 0.26-0.75, I2 62%, eight studies included). Pooled limb salvage rates after direct and indirect revascularization were at 1 year 86.2% vs. 77.8% and at 2 years 84.9% vs. 70.1%, respectively. The analysis of three studies reporting only on patients with diabetes confirmed the benefit of direct revascularization in terms of limb salvage (HR 0.48, 95% CI: 0.31-0.75, I2 0%).

Study	Population	Intervention	Comparison	Methodological Quality	Results
Sumpio, 2013[84]	Systematic review of 11 case series (1616 patients, 1757 limbs)	Revascularization		Mostly retrospective case series at increased risk of bias	Ten studies compared DR and IR. Five studies reported limb salvage rate was higher with DR than IR (93% vs 72%; P = .02) Five out of eight studies who reported wound healing rates found a significant increase with DR when compared with IR; however, length of follow-up varied among these studies (Table I). Mean time to healing was not significantly different in DR compared with IR when analyzed by three studies. One study found a significant increase in amputation-free survival in DR when compared with IR (evaluated by three studies24, 26, 27). Seven studies, with a predominantly diabetic population, reported limb salvage as a primary outcome, and three found a significant increase with DR compared with IR.
Azuma, 2012[85]	228 patients (249 limbs) with CLTI	Bypass	NA	Retrospective consecutive case series	The complete healing of ischaemic wounds was achieved in 211 limbs (84.7%). ESRD (odds ratio (OR) 0.127, p < 0.001), diabetes (OR 0.216, p = 0.030), Rutherford category 6 (R6) with heel ulcer/gangrene (OR 0.134, p < 0.001), R6 except heel (OR 0.336, p = 0.025) and low albuminaemia (OR 0.387, p = 0.049) were negative predictors of wound healing. Regarding the angiosome, the healing rate in the indirect revascularisation (IR) group was slower than in the direct

Study	Population	Intervention	Comparison	Methodological Quality	Results
					revascularisation (DR) group, especially in patients with ESRD ($p < 0.001$). However, the healing rates of the DR and IR groups were similar after minimising background differences with propensity score methods ($p = 0.185$).
		Recommendation 6.39			
Almasri, 2017[80]	44 studies that enrolled 8,602 patients with chronic limb threatening ischemia	All infrainguinal revascularization procedures	NA	Noncomparative meta-analysis	Prosthetic bypass outcomes were notably inferior to vein bypass in terms of amputation and patency outcomes, especially for below knee targets at two years and beyond. Drug eluting stents demonstrated improved patency over bare metal stents in infra-popliteal arteries (primary patency: 73% vs. 50% at 1 year, and was at least comparable to balloon angioplasty (66% primary patency), albeit within an anatomically restricted cohort of CLTI patients. Survival, major amputation and amputation-free survival at two years were broadly similar between endovascular interventions and vein bypass, with prosthetic bypass having higher rates of limb loss
Schillinger, 2006[86]	104 patients with severe claudication or CLTI due to stensosi/occlusion of the superficial femoral artery	Stenting	angioplasty	RCT	Secondary stenting was performed in 17 of 53 patients (32 percent) in the angioplasty group, in most cases because of a suboptimal result after angioplasty. At 6 months, the rate of restenosis on angiography was 24 percent in the

Study	Population	Intervention	Comparison	Methodological Quality	Results
					stent group and 43 percent in the angioplasty group (P=0.05); at 12 months the rates on duplex ultrasonography were 37 percent and 63 percent, respectively (P=0.01). Patients in the stent group were able to walk significantly farther on a treadmill at 6 and 12 months than those in the angioplasty group.
Saxon, 2008[87]	197 patients with symptomatic PAD of superficial femoral artery	Percutaneous transluminal angioplasty	Angioplasty plus stent-graft	Multicenter RCT	The stent-graft group had a significantly higher technical success rate (95% vs 66%, P < .0001) and 1-year primary vessel patency rate at duplex ultrasonography (65% vs 40%, P = .0003). A patency benefit was seen for lesions at least 3 cm long. At 12 months, chronic limb ischemia status was 15% further improved for the stent-graft group (P = .003). There were no significant differences between treatment groups with regard to the occurrence of early or late major adverse events.
Dake, 2011[88]	474 patients with femoropopliteal PAD (236 primary drug-eluting stent; 238 angioplasty)	Drug-eluting stent	PTA, provisional bare-metal stent	Multinational RCT	One hundred twenty patients had acute PTA failure and underwent secondary random assignment to provisional DES (n=61) or BMS (n=59). Primary end points were the 12-month rates of event-free survival and patency in the primary DES and PTA groups. Compared with the PTA group, the primary DES group exhibited superior 12-month event-free

Study	Population	Intervention	Comparison	Methodological Quality	Results
					survival (90.4% versus 82.6%; P=0.004) and primary patency (83.1% versus 32.8%; P<0.001), satisfying the primary hypotheses. In the secondary evaluations, (1) the primary DES group exhibited superior clinical benefit compared with the PTA group (88.3% versus 75.8%; P<0.001), (2) the provisional DES group exhibited superior primary patency (89.9% versus 73.0%; P=0.01) and superior clinical benefit (90.5% and 72.3%, P=0.009) compared with the provisional BMS group, and (3) the stent fracture rate (both DES and BMS) was 0.9% (4/457).
Rosenfield, 2015[89]	476 patients with symptomatic intermittent claudication or ischemic pain while at rest and angiographically significant atherosclerotic lesions	angioplasty with a paclitaxel-coated balloon	Standard angioplasty	Single blinded, multicenter RCT	At 12 months, the rate of primary patency among patients who had undergone angioplasty with the drug-coated balloon was superior to that among patients who had undergone conventional angioplasty (65.2% vs. 52.6%, P=0.02). The proportion of patients free from primary safety events was 83.9% with the drug-coated balloon and 79.0% with standard angioplasty (P=0.005 for noninferiority). There were no significant between-group differences in functional outcomes or in the rates of death, amputation, thrombosis, or reintervention.
Recommendation 6.42					

Study	Population	Intervention	Comparison	Methodological Quality	Results
Mills 1992[90]	214 consecutive infrainguinal bypass grafts (209 reversed-vein and 5 polytetrafluoroethylene grafts)	duplex ultrasonography	NA	Prospective evaluation of consecutive sample, unblinded and not adjusted	Thirty-day primary patency was 99% (129 of 130) for femoropopliteal grafts and 93% (78 of 84) for femorodistal grafts. Secondary patency was 100% (130 of 130) and 96% (81 of 84), respectively. Primary patency was 89% (16 of 18) for those grafts that required intraoperative revision based on arteriographic findings.
Bandyk 1994[91]	368 patients after carotid endarterectomy, infrainguinal vein bypass or visceral/renal reconstruction	duplex ultrasonography	NA	Uncontrolled and nonrandomized series	Duplex scanning identified technical (residual plaque, stricture) or intrinsic defects (platelet thrombus, distal thrombosis) requiring revision in 37 (10%) of the reconstructions. Low (< 0.5%) complication rate
Recommendation 7.1					
Ubbink, 2013[92]	Six studies comprising nearly 450 patients with inoperable chronic critical leg ischaemia	Spinal cord stimulation	Standard care	Controlled nonblinded studies	Overall, no significantly different effect on ulcer healing was observed with the two treatments. Complications of SCS treatment consisted of implantation problems (9%, 95% CI 4 to 15%) and changes in stimulation requiring re-intervention (15%, 95% CI 10 to 20%). Infections of the lead or pulse generator pocket occurred less frequently (3%, 95% CI 0 to 6%). Overall risk of complications with additional SCS treatment was 17% (95% CI 12 to 22%), indicating a number needed to harm of 6 (95% CI 5 to 8).Average overall costs (one study) at two years were EUR 36,500 (SCS group) and EUR 28,600

Study	Population	Intervention	Comparison	Methodological Quality	Results
					(conservative group). The difference (EUR 7900) was significant (P < 0.009).
Recommendation 7.2					
Karanth, 2016[93]	Cochrane review showing no trials. Critical lower limb ischemia due to non-reconstructable peripheral arterial disease.	Lumbar sympathectomy	Standard care	NA	No trials
Recommendation 7.3					
Abu Dabrh, 2015[94]	19 studies enrolling 2779 patients with CLI	Medical therapies (prostaglandin E1 and angiogenic growth factors) and devices (pumps and spinal cord stimulators)	Control interventions	Meta-analysis of randomized and nonrandomized studies at increased risk of bias	None of the nonrevascularization-based treatments were associated with a significant effect on mortality. Intermittent pneumatic compression (OR, 0.14; 95% CI, 0.04-0.55) and spinal cord stimulators (OR, 0.53; 95% CI, 0.36-0.79) were associated with reduced risk of amputation. The quality of evidence was low because of increased risk of bias and imprecision.
Recommendation 7.4					
Vietto 2018[95]	33 Randomized controlled trials with 4477 participants	Prostanoids	Other agents or placebo	Meta-analysis of randomized trials at increased risk of bias	Low-quality evidence that suggests no clear difference in the incidence of cardiovascular mortality between patients receiving prostanoids and those given placebo (risk ratio (RR) 0.81, 95% confidence interval (CI) 0.41 to 1.58). High-quality evidence suggests that prostanoids have no effect on the incidence of total amputations when compared with placebo (RR 0.97, 95% CI 0.86 to 1.09).

Study	Population	Intervention	Comparison	Methodological Quality	Results
					Adverse events were more frequent with prostanoids than with placebo (RR 2.11, 95% CI 1.79 to 2.50; moderate-quality evidence)
Recommendation 7.5					
Smith 2012[96]	8 Trials enrolling 269 participants	Naftidrofuryl	Other agents or placebo	Meta-analysis of randomized trials at increased risk of bias	The effect of naftidrofuryl was statistically non-significant on pain, rest pain, skin necrosis or mean ankle systolic pressure
Recommendation 7.6					
Kranke 2015[97]	12 Trials enrolling 269 participants	Hyperbaric oxygen therapy	Usual care	Meta-analysis of randomized trials at increased risk of bias	Increased ulcer healing rate in diabetics without significant effect on other outcomes. Data specifically in CLI were limited
Game, 2016[98]	Systematic review of 30 studies, including 13 hyperbaric oxygen therapy trials	Hyperbaric oxygen therapy		11 RCTs and 2 retrospective cohort studies, at increased risk of bias	Studies have conflicting results. It is not yet clear which patients would benefit from HBOT.
Santema, 2017[99]	120 patients with diabetes with an ischemic wound	Hyperbaric oxygen therapy	Usual care	RCT	After 12 months, 28 index wounds were healed in the SC group vs. 30 in the SC+HBOT group (RD 3% [95% CI -14 to 21]). AFS was achieved in 41 patients in the SC group and 49 patients in the SC+HBOT group (RD 13% [95% CI -2 to 28]). In the SC+HBOT group, 21 patients (35%) were unable to complete the HBOT protocol as planned. Those who did had significantly fewer major amputations and higher AFS (RD for AFS 26% [95% CI 10-38]).
Recommendation 8.1					
Abu Dabrh, 2015[94]	19 studies enrolling 2779 patients with CLI	Medical therapies (prostaglandin E1 and angiogenic growth factors)	Control interventions	Meta-analysis of randomized and nonrandomized	None of the nonrevascularization-based treatments were associated with a significant effect on

Study	Population	Intervention	Comparison	Methodological Quality	Results
		and devices (pumps and spinal cord stimulators)		studies at increased risk of bias	mortality. Intermittent pneumatic compression (OR, 0.14; 95% CI, 0.04-0.55) and spinal cord stimulators (OR, 0.53; 95% CI, 0.36-0.79) were associated with reduced risk of amputation. The quality of evidence was low because of increased risk of bias and imprecision.
Peeters Weem, 2015[100]	Meta-analysis of 10 studies (499 patients)	bone marrow derived cell therapy	Placebo	Randomized controlled trials	No significant differences were observed in major amputation rates (relative risk [RR] 0.91; 95% confidence interval [CI] 0.65-1.27), survival (RR 1.00; 95% CI 0.95-1.06), and amputation free survival (RR 1.03; 95% CI 0.86-1.23) between the cell treated and placebo treated patients. The ankle brachial index (mean difference 0.11; 95% CI 0.07-0.16), transcutaneous oxygen measurements (mean difference 11.88; 95% CI 2.73-21.02), and pain score (mean difference -0.72; 95% CI -1.37 to -0.07) were significantly better in the treatment group than in the placebo group.
Recommendation 9.1					
Elsherif 2017[101]	223 diabetic patients who underwent either digital or transmetatarsal amputation	Transmetatarsal amputation	Digital amputation	Nonrandomized comparative observational study, consecutive sample	The median time to major amputation was (400 ± IQR 1205 days) in the digital amputation group, compared to 690 ± IQR 891 days in the transmetatarsal amputation group (P = 0.974). 29.9% of digital amputations and 15.7% of transmetatarsal amputations in diabetic patients,

Study	Population	Intervention	Comparison	Methodological Quality	Results
					required minor amputations or revision procedures (P = 0.04). Median length of hospital stay was (20 days, IQR 27) in the digital group and (17 days, IQR17) in the transmetatarsal amputation group (P = 0.17). Need for re-admission was 48.1% in digital patients compared to 50% in transmetatarsal amputation patients (P = 0.81). Quality of time spent without symptoms of disease or toxicity of treatment (Q-TWiST) was (315 days, IQR 45) in digital group and (346 days, IQR 48) in the transmetatarsal amputation patients (P = 0.099)
Recommendation 9.2					
Siracuse 2015[102]	110,279 patients undergoing major vascular surgery	Do Not Resuscitate" Status	No DNR	Nonrandomized sample from National Surgical Quality Improvement Project database. Propensity score matching, no blinding	Compared with a matched cohort of "high-risk" non-DNR patients, those with DNR orders suffered equivalent rates of postoperative morbidity, but markedly increased mortality
Aziz 2015[103]	16,678 patients underwent emergency vascular operations	Do Not Resuscitate" Status	No DNR	Nonrandomized sample from National Surgical Quality Improvement Project database. Propensity score matching, no blinding	DNR patients were more likely to have higher rates of graft failure (8.7% vs 2.4%; adjusted P < .01) and failure to wean from mechanical ventilation (14.9 % vs 9.9%; adjusted P < .001). DNR status was associated with a 2.5-fold rise in 30-day mortality (35.0% vs 14.0%; 95% confidence interval, 1.7-2.9; adjusted P < .001)
Recommendation 9.3					

Study	Population	Intervention	Comparison	Methodological Quality	Results
Reed 2008[104]	33 Patients who had undergone below-knee or above-knee amputation after failed lower extremity revascularization	NA	NA	Survey with 39% nonresponse rate	Eighty-five percent (28 of 33 patients) of amputees would do everything to save the leg if faced with a similar scenario. Fifty-four percent (18/33) of patients actively used a prosthesis, and 91% (30/33) resided at home
Recommendation 9.4					
Rollins 1985[105]	Fifty-four patients underwent 56 profundaplasties for limb salvage	NA	NA	Uncontrolled surgical case series	After profundaplasty, ischemic ulcers healed in 9 of 17 (53%) patients. Rest pain was relieved in 6 of 19 (32%) and areas of ischemic necrosis healed in 7 of 20 (35%). Cumulative patency of the deep femoral artery was 49% at 3 years but fell to 21% at 5 years, whereas cumulative limb salvage was 49% and 36%, respectively. Eleven of the required 28 amputations were performed in the immediate postoperative period. Profundaplasty was used to lower the amputation level and preserve the knee joint in six patients. The other five early amputations occurred in severely ischemic limbs without distal vessels suitable for bypass. The profundaplasty remained patent in all 19 patients who underwent below-knee amputation and 16 (84%) became ambulatory with a prosthesis
Miksic 1986[106]	282 profunda femoris artery reconstructions	NA	NA	Uncontrolled surgical case series	An inflow correction was necessary in 60.3% of profunda reconstructions. Factors that bear on the success or failure of

Study	Population	Intervention	Comparison	Methodological Quality	Results
					profundaplasty were evaluated. These were aorto-iliac inflow, the extent of disease in the profunda femoris artery, the run-off in the distal popliteal-tibial system and the extent of the ischemic lesion. Of the failures most were due to established gangrene, obstructions throughout the whole length of the profunda or patients with a poor popliteal-tibial run-off system. The cumulative limb salvage at two years was 86.8% in limbs subjected to inflow correction procedure and profundaplasty but only in 56.5% of repair of the profunda alone
Recommendation 9.5					
Ayoub 1993[107]	32 patients with thru-knee amputations for ischemia	NA	NA	Uncontrolled consecutive surgical case series	Average length of stay was 8.7 days. One patient required a revision to above-the-knee amputation. There were no other major complicatnois.
Taylor 2008[108]	309 below-knee amputation patients	NA	NA	Uncontrolled consecutive surgical case series	Patients with coronary artery disease [odds ratio (OR), 0.465; 95% CI, 0.289-0.747], cerebrovascular disease (OR, 0.389; 95% CI, 0.154-0.980), and impaired ambulatory ability before BKA (OR, 0.310; 95% CI, 0.154-0.623) were less likely to have a successful outcome (wound healing, maintenance of ambulation and survival for at least 6 months) with below-knee amputation. Patients with impaired ambulation combined with another factor had only a 20-23%

Study	Population	Intervention	Comparison	Methodological Quality	Results
					probability of successful outcome and patients with all three had a 10.4% probability of success.
Recommendation 9.6					
Webster 2012[109]	individuals undergoing their first major lower-limb amputation because of vascular disease and/or diabetes	NA	NA	Uncontrolled surgical case series	At 4 mo, unsuccessful prosthetic fitting was significantly associated with depression, prior arterial reconstruction, diabetes, and pain in the residual limb. At 12 mo, 92% of all subjects were fit with a prosthetic limb and individuals with transfemoral amputation were significantly less likely to have a prosthesis fit. Age older than 55 yr, diagnosis of a major depressive episode, and history of renal dialysis were associated with fewer hours of prosthetic walking
Recommendation 9.7					
Glaser 2013[110]	1715 Patients undergoing lower extremity amputation (exclusive of trauma or tumor)	NA	NA	Uncontrolled surgical case series	Cox proportional hazards regression analysis revealed end-stage renal disease (hazard ratio [HR], 3.9; 95% confidence interval [CI], 2.3-6.5), chronic renal insufficiency (HR, 2.2; 95% CI, 1.5-3.3), atherosclerosis without diabetic neuropathy (HR, 2.9; 95% CI, 1.5-5.7), atherosclerosis with diabetic neuropathy (HR, 9.1; 95% CI, 3.7-22.5), and initial major amputation (HR, 1.8; 95% CI, 1.3-2.6) were independently predictive of subsequent contralateral major amputation
Bradley 2006[111]	107 vascular amputees (mean age 70) referred for prosthesis provision	NA	NA	Cross sectional study, unblinded or adjusted	41% were prescribed a statin and 39% were prescribed a statin and 60% an anti-platelet agent. While

Study	Population	Intervention	Comparison	Methodological Quality	Results
					39% of these patients were on both drugs, 32% had been prescribed neither
Recommendations 10.1, 10.2, 10.3, 10.4, 10.5 (also see evidence tables for 4.7, 4.8)					
Bedenis 2015[112]	16 studies with 5683 randomised participants. Nine different treatment groups were evaluated: aspirin (ASA) or aspirin and dipyridamole (ASA/DIP) versus placebo or nothing (six studies); ASA or ASA/DIP versus pentoxifylline (two studies); ASA/DIP versus indobufen (one study); ASA or ASA/DIP versus vitamin K antagonists (two studies); ASA/DIP versus low molecular weight heparin (one study); ticlopidine versus placebo (one study); ASA versus prostaglandin E1 (one study); ASA versus naftidrofuryl (one study); and clopidogrel and ASA versus ASA alone (one study)	Antiplatelets	Other approaches	Meta-analysis of trials at low to moderate risk of bias	Improved graft patency in the ASA or ASA/DIP treatment group, odds ratio (OR) 0.42 (95% confidence interval (CI) 0.22 to 0.83; P = 0.01; 952 participants).
Abbruzzese 2004[113]	172 patients underwent 189 primary autogenous infraing uinal arterial reconstructions	Statins	No statins	Retrospective comparative study, not blinded, adjusted analysis	Perioperative mortality (2.6%) and major morbidity (3.2%) were not different between groups. There was no difference in primary patency (74% +/- 5% vs 69% +/- 6%; P =.25), limb salvage (92% +/- 3% vs 90% +/- 4%; P =.37), or survival (69% +/- 5% vs 63% +/- 5%; P =.20) at 2 years. However,

Study	Population	Intervention	Comparison	Methodological Quality	Results
					patients on statins had higher primary-revised (94% +/- 2% vs 83% +/- 5%; P <.02) and secondary (97% +/- 2% vs 87% +/- 4%; P <.02) graft patency rates at 2 years. Of all factors studied by univariate analysis, only statin use was associated with improved secondary patency (P =.03) at 2 years. This was confirmed by multivariate analysis
Henke, 2004[114]	293 patients (338 infrainguinal bypass procedures	NA	NA	Retrospective case series	Statin drugs were taken by 56% of patients, ACE inhibitors by 54% of patients, and antiplatelet agents or warfarin sodium (Coumadin) by 93% of patients. Statin drug use was independently associated with increased graft patency (odds ratio [OR], 3.7; 95% confidence interval [CI], 2.1-6.4) and with decreased amputation rate (OR, 0.34; 95% CI, 6.15-0.77). Kaplan-Meier analysis showed that only ACE inhibitors were associated with lower mortality (P =.05)
Suckow, 2015[115]	2067 infrainguinal bypass patients, from the Vascular Study Group of New England registry (67% with CLTI)	NA	NA	Retrospective analysis of prospectively collected data	Despite higher comorbidity burdens, long-term survival was better for patients taking statins in crude (risk ratio [RR], 0.7; P < .001), adjusted (hazard ratio, 0.7; P = .001), and propensity-matched analyses (hazard ratio, 0.7; P = .03). In subgroup analysis, a survival advantage was evident in patients on statins with CLI (5-year survival rate, 63% vs 54%; log-rank, P = .01) but not claudication (5-year

Study	Population	Intervention	Comparison	Methodological Quality	Results
					survival rate, 84% vs 80%; log-rank, P = .59). Statin therapy was not associated with 1-year rates of major amputation (12% vs 11%; P = .84) or graft occlusion (20% vs 18%; P = .58) in CLI patients. Perioperative myocardial infarction occurred more frequently in patients on a statin in crude analysis (RR, 2.2; P = .01) but not in the matched cohort (RR, 1.9; P = .17).
Brown, 2008[116]	Systematic review of randomized and nonrandomized studies of patients undergoing infrainguinal bypass surgery	Antiplatelet treatment	No antiplatelet treatment	Moderate risk of bias overall	The administration of a variety of platelet inhibitors resulted in improved venous and artificial graft patency when compared to no treatment. However, analyzing patients for graft-type indicated that those patients receiving a prosthetic graft were more likely to benefit from administration of platelet inhibitors than patients treated with venous grafts.
Willigendael, 2005[117]	Meta-analysis of data from 29 studies	NA	NA	Moderate risk of bias overall	The effect of smoking on graft patency in the randomized clinical trials and other prospective studies had a 3.09-fold (2.34 to 4.08; P < .00001) increase in graft failure. There is a dose-response relationship, with decreased patency in heavy smokers compared with moderate smokers. Smoking cessation restores patency rates toward the never smokers group.

Study	Population	Intervention	Comparison	Methodological Quality	Results
Hobbs, 2003[118]	Review of systematic reviews on smoking cessation strategies	Smoking cessation interventions	Usual care	Moderate risk of bias overall	Cochrane reviews have shown benefits of NRT, as well as a small but significant benefit from brief physician advice compared to no advice (odds ratio [OR] 1.69). More frequent advice may be marginally more effective.
Belch, 2010[119]	851 patients undergoing unilateral, below-knee bypass graft	Clopidogrel plus aspirin	Placebo plus aspirin	Randomized placebo-controlled multinational trial	The primary efficacy endpoint was a composite of index-graft occlusion or revascularization, above-ankle amputation of the affected limb, or death. In the overall population, the primary endpoint occurred in 149 of 425 patients in the clopidogrel group vs 151 of 426 patients in the placebo (plus ASA) group (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.78-1.23). In a prespecified subgroup analysis, the primary endpoint was significantly reduced by clopidogrel in prosthetic graft patients (HR, 0.65; 95% CI, 0.45-0.95; P = .025) but not in venous graft patients (HR, 1.25; 95% CI, 0.94-1.67, not significant [NS]). A significant statistical interaction between treatment effect and graft type was observed (P(interaction) = .008). Although total bleeds were more frequent with clopidogrel, there was no significant difference between the rates of severe bleeding in the clopidogrel and placebo (plus ASA) groups (2.1% vs 1.2%).

Study	Population	Intervention	Comparison	Methodological Quality	Results
Gassman, 2014[120]	165 bypasses in patients with multiple comorbidities (79% CLTI)	Preoperative aspirin	NA	Case series	Pre- and postoperative aspirin usage was associated with increased two-year secondary prosthetic graft patency over control (preoperative: 78% versus 44%, P < 0.002 and postoperative: 72% versus 50%, P < 0.01). Preoperative aspirin usage was associated with an improvement in the rate of amputation (odds ratio [OR] = 0.44 [95% CI 0.198-0.997]) and stenosis (OR = 0.45 [95% CI 0.217-0.956]).
Bhatt, 2006[121]	15,603 patients with clinical evident cardiovascular disease or multiple risk factors	Clopidogrel plus low dose aspirin	Placebo plus low dose aspirin	Large randomized controlled trial	The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The rate of the primary efficacy end point was 6.8 percent with clopidogrel plus aspirin and 7.3 percent with placebo plus aspirin (relative risk, 0.93; 95 percent confidence interval, 0.83 to 1.05; P=0.22). The respective rate of the principal secondary efficacy end point, which included hospitalizations for ischemic events, was 16.7 percent and 17.9 percent (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.995; P=0.04), and the rate of severe bleeding was 1.7 percent and 1.3 percent (relative risk, 1.25; 95 percent confidence interval, 0.97 to 1.61 percent; P=0.09). The rate of the primary end point among patients with multiple risk factors was 6.6

Study	Population	Intervention	Comparison	Methodological Quality	Results
					percent with clopidogrel and 5.5 percent with placebo (relative risk, 1.2; 95 percent confidence interval, 0.91 to 1.59; P=0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel (3.9 percent vs. 2.2 percent, P=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9 percent with clopidogrel and 7.9 percent with placebo (relative risk, 0.88; 95 percent confidence interval, 0.77 to 0.998; P=0.046).
Cassar, 2005[122]	132 patients with claudication undergoing endovascular revascularization	Clopidogrel plus aspirin	Placebo plus aspirin	Double-blinded, placebo-controlled RCT	Clopidogrel plus aspirin inhibits platelet function more than aspirin alone. Platelet function in the clopidogrel group was significantly suppressed compared with baseline at 1 h, 24 h and 30 days after endovascular intervention (stimulated fibrinogen binding by 53.9, 51.7 and 57.2 per cent respectively; all P < 0.001).
Strobl 2013 and Tepe 2012[123, 124]	80 patients with peripheral artery disease endovascularly treated	pre- and postinterventional therapy with aspirin and clopidogrel	aspirin and placebo	Blinded trial at low risk of bias	At 6 months, clopidogrel patients had significantly lower rates of target lesion revascularization compared to placebo patients [2 (5%) vs. 8 (20%), p=0.04]. After stopping clopidogrel/placebo after 6 months, there was no significant difference in target lesion revascularization at 12 months after treatment [9 (25%) clopidogrel vs. 12 (32.4%) placebo, p=0.35]. Mortality was 0 vs. 1 in the placebo group at 6 months

Study	Population	Intervention	Comparison	Methodological Quality	Results
					(p=0.32) and 0 vs. 3 at 12 months (p=0.08). Dual antiplatetet therapy reduces peri-interventional platelet activation and improves functional outcome without higher bleeding complications.
Cassar 2005[122]	132 Patients after lower limb angioplasty	clopidogrel and aspirin	placebo and aspirin,	Blinded trial at low risk of bias	clopidogrel and aspirin inhibited platelet function more than aspirin alone in patients with claudication before and after angioplasty.
Recommendation 10.10					
Mills 2001[125]	156 autogenous infrainguinal vein grafts in 142 patients	Duplex ultrasound surveillance	NA	Uncontrolled or blinded	The incidence of graft thrombosis was 3% per year (mean follow-up, 27.5 months). Intermediate lesions developed in 32 grafts (20%). Among these 32 grafts with intermediate stenoses, 63% progressed to critical and were revised, and 32% resolved or stabilized
Recommendation 10.11					
Landry 2002[126]	330 surgical graft revisions were performed on 259 extremities in 245 patients	Reversed lower-extremity vein grafts	NA	Retrospective noncomparative analysis	The assisted primary patency rate of all grafts, the limb-salvage rate for patients undergoing surgery for limb-salvage indications, and the survival rate of all patients were 87.4%, 88.7%, and 72.4%, respectively, 5 years after the original bypass grafting procedure, 85.7%, 83.4%, and 67.8%, respectively, 7 years after the original bypass grafting procedure, and 80.4%, 75.4%, and 53.4%, respectively, 10 years after the original bypassgrafting procedure.

Study	Population	Intervention	Comparison	Methodological Quality	Results
					A total of 180 revisions (55%) were performed during the first year, 110 (33%) between the first year and the fifth year, and 40 revisions (12%) were performed on grafts older than 5 years. LEVGs revised within the first year after bypass grafting had lesions within the graft in 78%, in the native arterial inflow in 10%, and in the native arterial outflow in 12%. This differed significantly from the location of lesions in revisions performed between 1 and 5 years and after 5 years (graft, 63% and 62%; inflow, 20% and 19%; outflow, 17% and 19%; P >.05, Chi-square)
Nguyen 2004[127]	188 vein grafts, from a total series of 1260 bypasses, undergoing revision of stenotic lesions	Revision procedures performed for repair of stenotic lesions in infrainguinal vein bypass grafts.	NA	Retrospective noncomparative series	There was no difference in patency rate for different revision procedures, type of vein graft, indication for the original procedure, or for patients with diabetes mellitus or renal disease. The overall limb salvage rate was 83.2% +/- 3.5% 5 years after graft revision. With COX proportional hazard analysis of time to failure of the revision procedure, the outflow level of the original bypass and the time of revision proved to be an important predictor of durability of the graft revision. Revision of popliteal bypass grafts resulted in a 60% 5-year primary patency rate, whereas revision of tibial grafts resulted in a 42% 5-year primary

Study	Population	Intervention	Comparison	Methodological Quality	Results
					patency rate (P = .004; hazard ratio [HR], 2.06). Five-year secondary patency rates were 90% and 76%, respectively (P = .009; HR = 3.43). The timing of the graft revision proved an additional predictor. Grafts revised within 6 months of the index operation had lower primary patency than those with later revisions (42.9% vs 80.7%, respectively; HR = 1.754; P = .0152)
Recommendation 10.12					
Bui 2012[128]	Ninety-four limbs (85 patients) underwent EVT for SFA-popliteal disease	NA	NA	Prospective nonrandomized study, consecutive sampling, unblinded	The initial scans were normal in 61 limbs (65%), and serial DU results remained normal in 38 (62%). In 17 limbs (28%), progressive stenoses were detected during surveillance. The rate of thrombosis in this subgroup was 10%. Moderate stenoses were detected in 28 (30%) limbs at initial scans; of these, 39% resolved or stabilized, 47% progressed to severe, and occlusions developed in 14%. Five (5%) limbs harbored severe stenoses on initial scans, and 80% of lesions resolved or stabilized. Progression to occlusion occurred in one limb (20%). The last DUS showed 25 limbs harbored severe stenoses; of these, 13 (52%) were in symptomatic patients and thus required reintervention regardless of DU findings. Eleven limbs (11%) eventually occluded. Sensitivity

Study	Population	Intervention	Comparison	Methodological Quality	Results
					and specificity of DUS to predict occlusion were 88% and 60%, respectively
Recommendation 10.13					
Humphries 2011[129]	122 infrainguinal interventions for CLI in 113 patients (53% male; mean age 71 years	early duplex	normal duplex	Nonrandomized prospective comparative study, unblinded or adjusted	Fifty patients had an abnormal early duplex and 40 patients had a normal duplex. In patients with a normal duplex ultrasound the amputation rate was 5% vs 20% in the group with an abnormal duplex (P = .04). Primary patency was 56% in the normal duplex group and 46% in the abnormal duplex group (P = .18). Early duplex ultrasound was able to identify a residual stenosis not seen on completion angiography in 56% of cases.
Recommendations 10.14, 10.15					
Elraiyah 2016[130]	19 interventional studies, of which 13 were randomized controlled trials, including data from 1605 patients with diabetic foot ulcers using an off-loading method	Offloading approaches	Usual care	The risk of bias in the included studies was moderate.	This analysis demonstrated improved wound healing with total contact casting over removable cast walker, therapeutic shoes, and conventional therapy. There was no advantage of irremovable cast walkers over total contact casting. There was improved healing with half-shoe compared with conventional wound care. Therapeutic shoes and insoles reduced relapse rate in comparison with regular footwear. Data were sparse regarding other off-loading methods

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Global Vascular Guideline on the Management of Chronic Limb Threatening Ischemia

Tables and Figures

Table 1.1. Classification schemes used for chronic limb ischemia and/or ulceration

Classification System	Ischemic Rest Pain	Ulcer	Gangrene	Ischemia	Infection	Key features and comments
Ischemia/PAD Classifications						
Fontaine (1954)	Yes (Class III/IV)	Class IV/IV - ulcer and gangrene grouped together	Class IV/IV - ulcer and gangrene grouped together	Cutoff values for CLI based on European consensus document: Ischemic rest pain > 2 weeks with AP < 50 mm Hg or TP < 30 mmHg Ulcer and gangrene: AP < 50 mm Hg, TP < 30 mm Hg, absent pedal pulses in patient with diabetes	No	Pure ischemia model No clear definitions of spectrum of hemodynamics; minimal description of wounds; infection omitted
Rutherford (1997)	Yes (Category 4/6)	Category 5 - minor tissue loss - nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Category 6 - major tissue loss extending above TM level, functional foot no longer salvageable (although in practice often refers to extensive gangrene, potentially salvageable foot with significant efforts)	Yes - cutoffs for "CLI" Category 4: Resting AP < 40 mm Hg; flat or barely pulsatile ankle or forefoot PVR; TP < 30 mmHg Category 5/6: AP < 60 mmHg; flat or barely pulsatile ankle or forefoot PVR; TP < 40 mmHg	No	Pure ischemia model PAD classification system includes milder forms of PAD (Categories 1-3). Categories 4-6 based on cutoff values for CLI; no spectrum of ischemia, doesn't acknowledge potential need for revascularization with < CLI cutoff depending on wound extent/infection; not intended for patients with diabetes; wound classes not sufficiently detailed; omits infection as a trigger
2nd Euro Consensus (1991)	yes; pain > 2 weeks requiring analgesia; AP ≤50 mmHg and/or TP ≤30 mmHg	yes, if AP ≤50 mmHg and/or TP ≤30 mmHg	yes, if AP ≤50 mmHg and/or TP ≤30 mmHg	One hemodynamic cutoff for ulcer and gangrene, with or without diabetes	No	Ischemia threshold too low, especially for patients with diabetes; wounds not graded; infection not considered

TASC I (2000)	yes, if ischemia criteria met	yes, if ischemia criteria met	yes, if ischemia criteria met	One hemodynamic cutoff, with no differentiation of diabetics from non-diabetics	No	Focused primarily on arteriographic anatomy without detailed stratification of the limb itself (wounds and infection not graded)
TASC 2 (2007)	yes, if AP < 50 mm Hg or TP < 30 mm HG	yes, if ischemia criteria met of AP < 70 mmHg or TP < 50 mmHg	yes, if ischemia criteria met of AP < 70 mmHg or TP < 50 mmHg	Yes, but noted "there is not complete consensus regarding the vascular haemodynamic parameters required to make the diagnosis of CLI"	No	Focused primarily on arteriographic anatomy without detailed stratification of the limb itself (wounds and infection not graded); issues with hemodynamic criteria noted
Diabetic Foot Ulcer Classifications						
Meggitt-Wagner (1976, 1981)	No	Grade 0: pre- or postulcerative lesion Grade 1: partial/full thickness ulcer Grade 2: probing to tendon or capsule Grade 3: deep ulcer with osteitis Grade 4: partial foot gangrene Grade 5: whole foot gangrene	Ulcer and gangrene grouped together; gangrene due to infection not differentiated from gangrene due to ischemia; also includes osteomyelitis	No	No for soft tissue component; included only as osteomyelitis	Orthopedic classification intended for Diabetic Feet No hemodynamics; Gangrene from infection not differentiated from that due to ischemia; Osteomyelitis included; soft tissue infection not separated from bone infection
University of Texas - UT (1998)	No	Yes: Grades 0 - III ulcers Grade 0: pre or postulcerative completely epithelialized lesion Grade I: superficial, not involving tendon, capsue or bone Grade II: penetrating to tendon/caspsule	No	Yes : Binary +/- based on ABI < 0.8	Yes +/- Wounds with frank purulence or ≥2 of the following (warmth, eythema, lymphangitis, edema, lymphadenopathy, pain, loss of	Primarily intended fors DFUs; includes validated ulcer categories; PAD and infection included, but only as +/- variable with no grades/spectrum

		Grade III: penetrating to bone or joint			function) considered infected	
S(AD)SAD System (1999)	No	Yes 0-3 based on area and depth Grade 0 skin intact Grade 1 superficial, < 1 cm2 Grade 2 peneterates to tendon, periosteum, joint capsule, 1-3 cm2 Grade 3 Lesions in bone or joint space, > 3cm2	No	Pulse palpation only, no objective hemodynamic testing	Yes 1 = no infection 2 = cellulitis 3 = osteomyelitis	Intended for DFUs; also includes neuropathy; does not mention gangrene; no hemodynamic information, perfusion assessment based on pulse palpation only
PEDIS (2004)	No	Yes- Grades 1-3 Grade 1: superficial full-thickness ulcer, not penetrating deeper than the dermis Grade 2: deep ulcer, penetrating below the dermis to subcutaneous structures involving fascia, muscle or tendon Grade 3: All subsequent layers of the foot involved including bone	No	Yes: 3 grades, "CLI" cutoff Grade 1: no PAD symptoms, ABI>0.9, TBI > 0.6, TcpO2 > 60 mm Hg Grade 2: PAD symptoms, ABI <0.9, AP > 50 mmHg, TP>30 mmHg, TcpO2 30-60 mmHg Grade 3: AP<50 mmHg, TP<30 mmHg, TcpO2<30 mmHg	Yes Grades 1-4 based on IDSA classification	Primarily intended for DFUs; ulcer grades validated; includes perfusion assessment, but with cutoff for "CLI"; gangrene not separately categorized; includes validated IDSA infection categories

		and/or joint (exposed bone, probing to bone)				
Saint Elian (2010)	No	Yes Grades 1-3 based on depth Grade 1: superficial wound disrupting entire skin Grade 2: Moderate or partial depth, down to fascia, tendon or muscle but not bone or joints Grade 3: Severe or total, wounds with bone or joint involvment Multiple categories including area, ulcer number, location and topography	No	Yes Grades 0-3 Grade 0: AP > 80 mmHg, ABI 0.9-1.2 Grade 1: AP 70-80 mmHg,ABI 0.7-0.89, TP 55-80 mmHg Grade 2: AP 55-69 mmHg, ABI 0.5-0.69, TP 30-54 mmHg Grade 3: AP < 55 mmHg, ABI < 0.5, TP < 30 mmHg	Yes Grades 0-3 Grade 0: none Grade 1: Mild. erythema 0.5-2 cm, induration, tenderness, warmth and purulence Grade 2: Moderate. erythema > 2 cm, abscess, muscle tendon, joint or bone infection Grade 3: severe. systemic response (similar to IDSA)	Detailed system intended only for DFUs; comprehensive ulcer classification system with hemodynamic categories for gradations of ischemia; gangrene not considered separately Infection system similar to IDSA

IDSA (2012)	No	No	No	No	Yes Uninfected, Mild, Moderate and Severe	Validated system for risk of amputation related to foot infection, but not designed to address wound depth/complexity or degree of ischemia
Recommended CLTI Classification						
SVS Wound, Ischemia, foot Infection (WIfI) Threatened Limb Classification (2014)	Yes if confirmed by hemodynamic criteria	Yes Grades 0-3 Grouped by depth, location and size and magnitude of ablative/wound coverage procedure required to achieve healing	Yes Grades 0-3 Grouped by extent, location and size and magnitude of ablative or wound coverage procedure required to achieve healing	Yes Ischemia Grades 0-3 hemodynamics with spectrum of perfusion abnormalities; no cutoff value for "CLI". Grade 0 unlikely to require revascularization	Yes , IDSA system (grades 0-3), grades corelate with amputation risk	Includes PAD +/- diabetes with a range of wounds, ischemia and infection, scaled from 0-3. No single cutoff for "CLI", as CLTI is considered as a spectrum of disease. Need for revascularization depends on degree of ischemia, wound and/or infection severity Ulcers/gangrene categorized based on extent and complexity of anticipated ablative surgery/ coverage
ABBREVIATIONS	AP = ankle pressure ABI= ankle-brachial index; TP = toe pressure PVR = pulse volume recording; TcpO2 = transcutaneous oxygen pressure mm Hg =	CLI = Critical Limb Ischemia; PAD = peripheral artery disease; DFU = Diabetic Foot Ulcer	UT = University of Texas IDSA = Infectious Disease Society of America SVS = Society for Vascular Surgery WIfI = Wound, Ischemia, foot Infection			

millimeters of mercury					

Table 1.2 One-year major limb amputation rate by SVS WIfI clinical stage

Study (year): # limbs at risk	Stage 1	Stage 2	Stage 3	Stage 4
Cull (2014)[68] **:** 151	37 (3%)	63 (10%)	43 (23%)	8 (40%)
Zhan (2015)[69]: 201	39 (0%)	50 (0%)	53 (8%)	59 (64%)*
Darling (2016)[71]: 551	5 (0%)	110(10%)	222 (11%)	213 (24%)
Causey (2016)[70]: 160	21 (0%)	48 (8%)	42 (5%)	49 (20%)
Beropoulis (2016)[163]: 126	29 (13%)	42 (19%)	29 (19%)	26 (38%)
Ward (2016)[166]: 98	5 (0%)	21 (14%)	14 (21%)	58 (34%)
Darling (2017)[164]: 992	12 (0%)	293 (4%)	249 (4%)	438 (21%)
Robinson (2017)[72]: 280	48 (2.1%)	67 (7.5%)	64 (7.8%)	83 (17%)
Mathioudakis (2017)[165]: 217	95 (4%)	33 (3%)	87 (5%)	64 (6%)
Tokuda (2018)[167]: 163	16 (0%)	30 (10%)	56 (10.7%)	61 (34.4%)
N = 2982 (weighted mean in %)	307 (3.2%)	757 (7.0%)	859 (8.7%)	1059 (23.3%)
Median (% 1-year major limb amputation)	0%	9 %	9.4 %	29%

[a] Number of limbs at risk in each WIfI Stage, with percent of amputations at 1 year in parentheses

[b] Means in totals (in parentheses) are weighted

[c] *= falsely elevated due to inadvertent inclusion of Stage 5 (unsalvageable) limbs

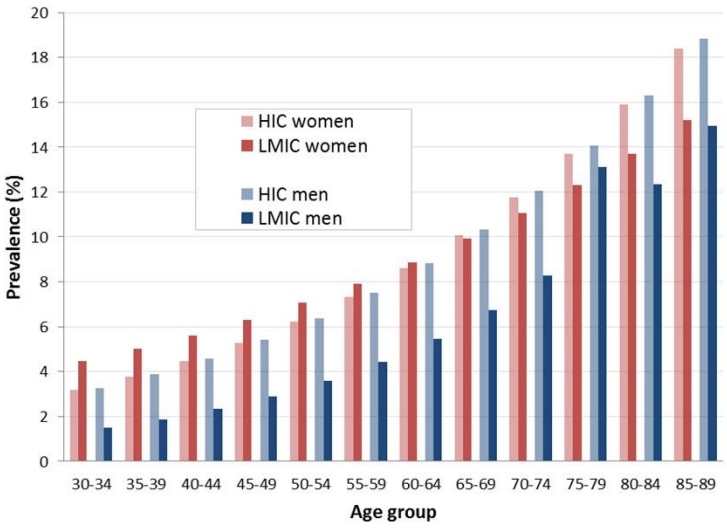


Figure 2.1. Prevalence of PAD (ABI <0.9) by age and sex in HIC and LMIC[1]

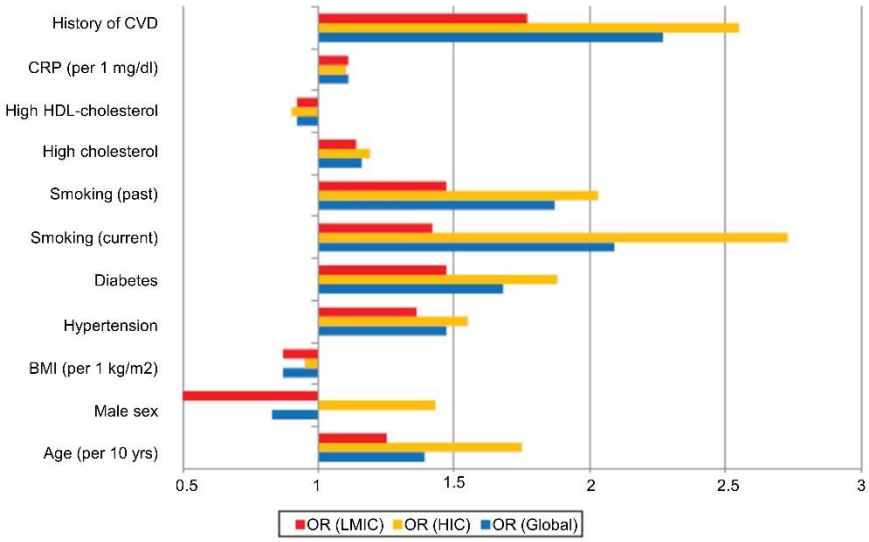


Figure 2.2. Odds ratios for PAD in HIC and LMIC (reprinted from Criqui et al[186])

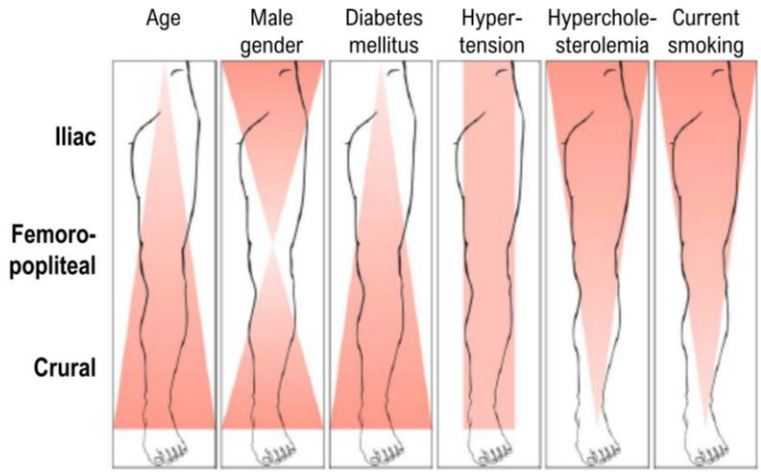


Figure 2.3. Association of risk factors with the level of atherosclerotic target lesions. Red overlay on the anatomic cartoon illustrates the association of risk factor with patterns of atherosclerotic disease[217] (reprinted from Diehm N et al[223])

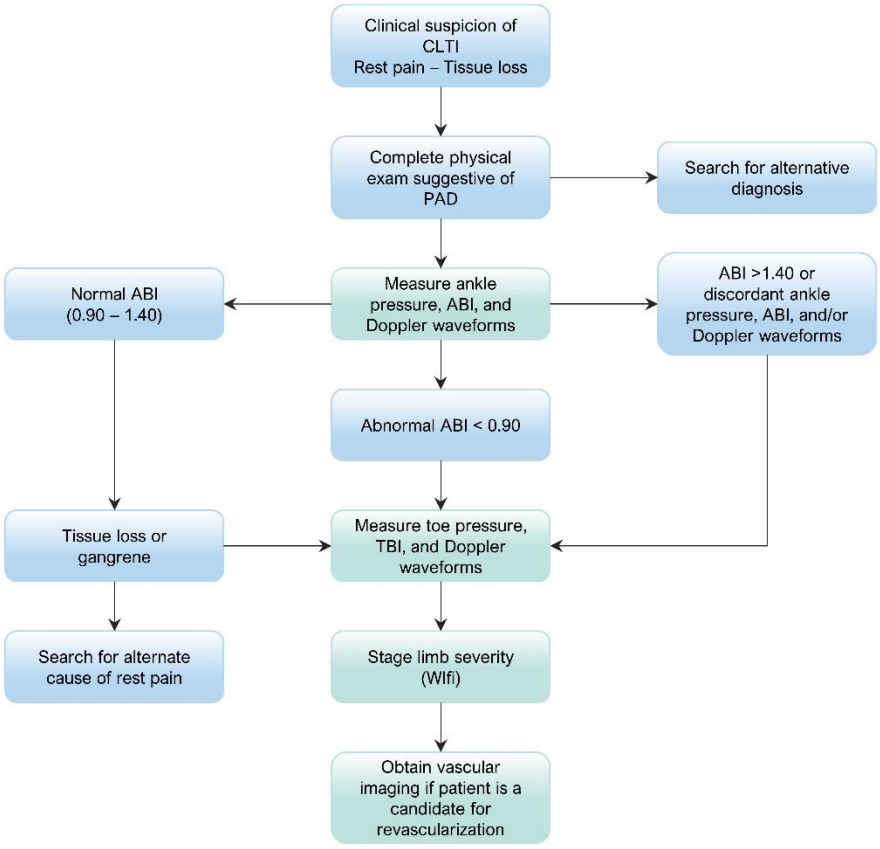


Figure 3.1. Flow diagram for the investigation of patients presenting with suspected CLTI.

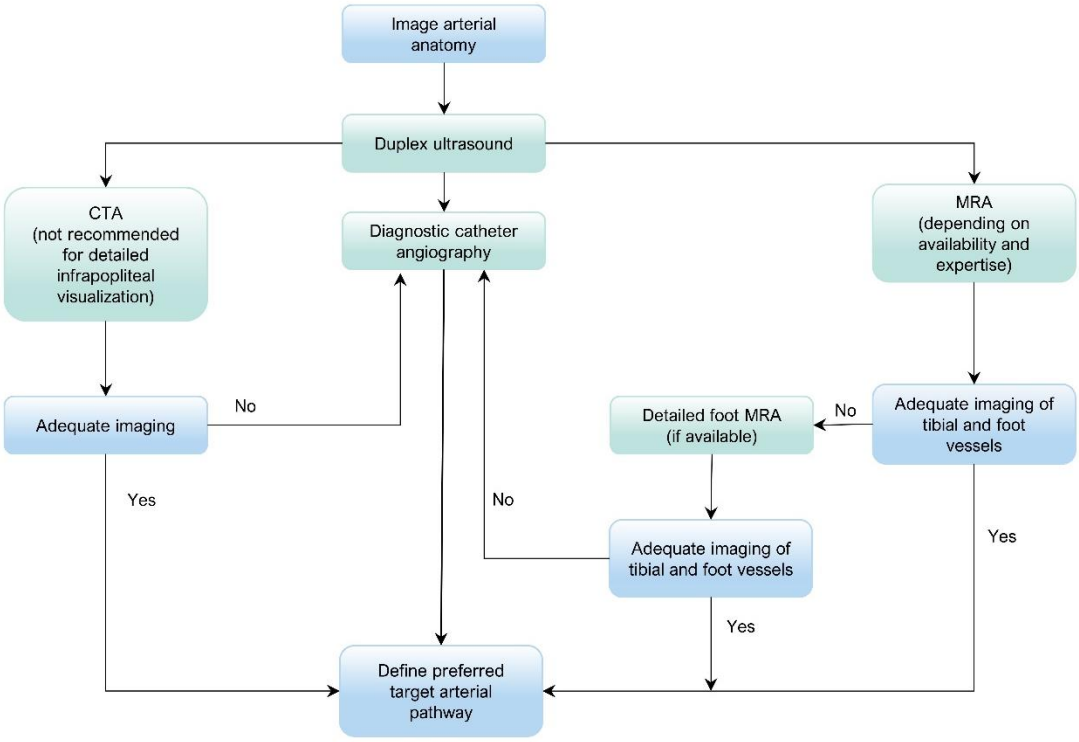


Figure 3.2. Suggested algorithm for anatomic imaging in patients with CLTI who are candidates for revascularization. In some cases it may be appropriate to proceed directly to angiographic imaging (CT, MR, or catheter) rather than duplex imaging.

Table 3.1. Comparison of methods of non-invasive testing in patients with CLTI

TECHNIQUES	ADVANTAGES	LIMITATIONS
Ankle pressure/ABI	• Simple, inexpensive, quick, widely applicable • Provides data to predict wound healing and limb survival. • Useful to monitor efficacy of therapeutic intervention	• Due to incompressible tibial arteries, may be falsely elevated or normal in patients with diabetes, renal insufficiency, or advanced age. • Does not provide localization of the disease
Toe pressure/TBI	• Simple, inexpensive, quick • Useful in the presence of small vessel artery disease. • Useful in non-compressible tibial arteries • Provides data to predict wound healing and limb survival. • Useful to monitor efficacy of therapeutic intervention	• Requires a hallux • Does not provide localization
Segmental pressures	• Useful in initial anatomical localization of CLTI disease. • Useful in creating therapeutic plan based on disease localization. • Provides data to predict wound healing and limb survival. • Useful to monitor efficacy of therapeutic intervention	• Not accurate in non-compressible tibial arteries.
$TcPO_2$	• Useful to assess microcirculation • Can predict wound healing • Maybe useful for monitoring efficacy of revascularization	• Limited accuracy in the presence of edema or infection • Requires skin heating to ≥40°C • Time-consuming • Limited data validation
Skin perfusion pressure	• Useful to assess microcirculation and wound healing potential • Maybe useful for monitoring efficacy of revascularization • Can be measured in a shorter time compared with $TcPO_2$	• Probe size and shape may affect measurements • Limited data validation

$TcPO_2$ = Transcutaneous oximetry. Adapted from Hirsch et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial diseases. *Circulation* 2006;113(11): e463—654.[247]

Table 3.2. Wound grading in WIfI

Grade	Ulcer	Gangrene
0	No ulcer	No gangrene
Clinical description: ischemic rest pain (requires typical symptoms + ischemia grade 3); no wound.		
1	Small, shallow ulcer on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene
Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.		
2	Deeper ulcer with exposed bone, joint or tendon; generally, not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits
Clinical description: major tissue loss salvageable with multiple (≥3) digital amputations or standard TMA ± skin coverage.		
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis ± calcaneal involvement
Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction (nontraditional transmetatarsal, Chopart, or Lisfranc amputation); flap coverage or complex wound management needed for large soft tissue defect		

Table 3.3. Ischemia grading in WIfI

Grade	ABI	Ankle systolic pressure	TP, $TcPO_2$
0	≥ 0.80	> 100 mm Hg	≥ 60 mm Hg
1	0.6-0.79	70-100 mm Hg	40-59 mm Hg
2	0.4-0.59	50-70 mm Hg	30-39 mm Hg
3	≤ 0.39	< 50 mm Hg	< 30 mm Hg

ABI, Ankle-brachial index; PVR, pulse volume recording; SPP, skin perfusion pressure; TP, toe pressure; $TcPO_2$, transcutaneous oximetry.

Flat or minimally pulsatile forefoot PVR = grade 3. Measure TP or $TcPO_2$ if ABI incompressible (> 1.3). Patients with diabetes should have TP measurements. If arterial calcification precludes reliable ABI or TP measurements, ischemia should be documented by $TcPO_2$, SPP, or PVR. If TP and ABI measurements result in different grades, TP will be the primary determinant of ischemia grade.

Table 3.4. Foot infection grading in WIfI

Clinical manifestation of infection	SVS	IDSA/PEDIS infection severity
No symptoms or signs of infection	0	Uninfected
Infection present, as defined by the presence of at least two of the following items: • Local swelling or induration • Erythema > 0.5 to ≤ 2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous secretion) Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis).	1	Mild
Local infection (as described above) with erythema > 2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis) and no systemic inflammatory response signs (as described below).	2	Moderate
Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: • Temperature > 38° or < 36°C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg • White blood cell count > 12,000 or < 4,000 cu/mm^3 or 10% immature (band) forms	3	Severe[a]

$PACO_2$, Partial pressure of arterial carbon dioxide; SIRS, systemic inflammatory response syndrome

[a] Ischemia may complicate and increase the severity of any infection. Systemic infection may sometimes manifest with other clinical findings, such as hypotension, confusion, vomiting, or evidence of metabolic disturbances, such as acidosis, severe hyperglycemia, new-onset azotemia.

Table 3.5. Clinical stages of major limb amputation risk based on WIfI classification

Risk of amputation	Proposed clinical stages	WIfI spectrum score
Very low	Stage 1	W0 I0 fI0,1
		W0 I1 fI0
		W1 I0 fI0,1
		W1 I1 fI 0
Low	Stage 2	W0 I0 fI2
		W0 I1 fI1
		W0 I2 fI0,1
		Wo I3 fI0
		W1 I0 fI2
		W1 I1 fI1
		W1 I2 fi0
		W2 I0 fI0/1
Moderate	Stage 3	W0 I0 fI3
		W0 I2 fI1,2
		W0 I3 fI1,2
		W1 I0 fI3
		W1 I1 fI2
		W1 I2 fI1
		W1 I3 fI0,1
		W2 I0 fI2
		W2 I 1 fI0,1
		W2 I2 fi0
		W3 I0 fi0,1
High	Stage 4	W0 I1,2,3 fI3
		W1 I1 fI3
		W1 I2,3 fI2,3
		W2 I0 fi3
		W2 I1 fI2,3
		W2 I2 fi1,2,3
		W2 I3 fI0,1,2,3
		W3 I0 fI2,3
		W3 I1,2,3 fI0,1,2,3

Clinical descriptors:
Stage 1: Minimal ischemia; no/minor tissue loss
Stages 2-4 reflect increasing stages of ischemia, wound, and infection
Stage 5 (not shown in table): Unsalvageable foot (most often due to wound extent or severity of infection)

Table 3.6. Comparison of different imaging modalities for patients with CLTI

TECHNIQUES	ADVANTAGES	LIMITATIONS
Duplex ultrasonography	• Non-invasive • Inexpensive • Quick, widely available worldwide • Useful to monitor efficacy of therapeutic intervention	• Highly operator dependent • Limitations to the visualization of iliac arteries due to body habitus, bowel gas • Calcification may produce incomplete examination • Most DUS studies were performed in mixed populations, thus, the validity of DUS imaging for CLTI patients alone is uncertain
CTA	• Non-invasive Excellent patient acceptance • Ability to evaluate previously stented arteries • Mostly applicable in patients with contraindications for MRA	• Image interference from calcified arteries • Potentially nephrotoxic contrast agents • Radiation exposure • Less reliable for imaging infrapopliteal vessels • Patients with CLTI who require a complete assessment of their lower extremity (including foot) arteries for planning a revascularization are under-represented in the current studies. The clinical value of CTA in the CLTI target population remains uncertain
MRA	• Non-invasive • Eliminates exposure to ionizing radiation • Unaffected by arterial calcification • Three-dimensional images of the entire arterial tree are presented in a maximum intensity projection format produced on a workstation • Easily produced arterial map aids planning of revascularization strategies	• Patients with pacemakers and defibrillators and some cerebral clips cannot be scanned safely • Tendency to overestimate stenosis • Metal clips can cause artefacts that mimic vessel occlusions • Venous contamination can obscure arteries below the knee
Catheter Angiography (DSA)	• Provides a complete map of the lower limb arteries • Images are easily displayed and interpreted by most physicians in charge of patients with CLTI • Selective catheter placement during lower extremity angiography enhances imaging, reduces contrast dose and enhances sensitivity in patients with CLTI	• Exposure to ionizing radiation and contrast media • Alternatively, carbon dioxide and magnetic resonance contrast agents (eg, gadolinium) can be used instead of conventional contrast media • Complications of catheterization despite improvements in catheter and guidewire technology

Table 5.1 Key definitions and assumptions in the GLASS staging system

Restoration of in-line flow to the ankle and foot is a primary goal
Target arterial path (TAP): the selected continuous route of in-line flow from groin to ankle. The TAP typically involves the least diseased infrapopliteal artery, but may be angiosome-based.
Limb-based patency (LBP): maintained patency of the TAP.
Inflow disease (aortoiliac and common femoral artery) is considered separately, and assumed corrected when using the infrainguinal staging system for clinical decision-making.
Grade within segment is determined by presence of any one of the defined descriptors within that grade (ie, the worst disease attribute within the segment defines grade).
Calcification considered only if severe; increases within segment grade by 1.
Inframalleolar (IM) disease (pedal) modifier: describes status of IM vessels (including terminal divisions of the peroneal artery) providing outflow into the foot.

[*]The generic case of rest pain is used as a default for defining TAP as the least diseased IP artery, or a specific IP target artery may be selected by the clinician, based on clinical circumstances (eg, angiosome-directed in setting of wounds).

Table 5.2. Inflow disease staging

A simplified staging system for inflow (aortoiliac and CFA) disease is suggested. Hemodynamically significant disease (> 50% stenosis) of the CFA is considered a key modifier (A/B).

I	Stenosis of the common and/or external iliac artery, chronic total occlusion of either common or external iliac artery (not both), stenosis of the infrarenal aorta; any combination of the above.
II	Chronic total occlusion of the aorta; chronic total occlusion of common and external iliac arteries; severe diffuse disease and/or small caliber (< 6 mm) common and external iliac arteries; concomitant aneurysm disease; severe diffuse in-stent restenosis in the aortoiliac system.
	A= no significant CFA disease; B= significant CFA disease (> 50% stenosis)

Table 5.5.3 Assignment of GLASS Stage. After selection of the TAP, the segmental FP and IP grades are determined from high-quality angiographic images. Using the table, the combination of FP and IP grades are assigned to GLASS Stages I-III, which correlate with technical complexity (low, intermediate, and high) of revascularization.

Infra-inguinal GLASS stage (I-III)

FP Grade	IP Grade 0	IP Grade 1	IP Grade 2	IP Grade 3	IP Grade 4
4	III	III	III	III	III
3	II	II	II	III	III
2	I	II	II	II	III
1	I	I	II	II	III
0	NA	I	I	II	III

Table 5.6.4 Descriptive summary of GLASS stages of infra-inguinal arterial disease.

	Estimated PVI Outcomes		
STAGE	**Technical Failure**	**1-year LBP**	**Anatomic pattern**
I	<10%	>70%	Short-intermediate length FP disease and/or short length IP disease. No/minimal popliteal disease
II	<20%	50-70%	Intermediate-long length FP disease, may include popliteal stenosis, and/or short-intermediate length IP disease.
III	>20%	<50%	Extensive FP or IP occlusions, alone or in combination with any disease in the other segment. Popliteal CTO.

PVI- peripheral [endo-]vascular intervention. **LBP-** limb-based patency.

Infra-malleolar/Pedal descriptor	
P0	Target artery crosses ankle into foot, with intact pedal arch
P1	Target artery crosses ankle into foot; absent or severely diseased pedal arch
P2	No target artery crossing ankle into foot

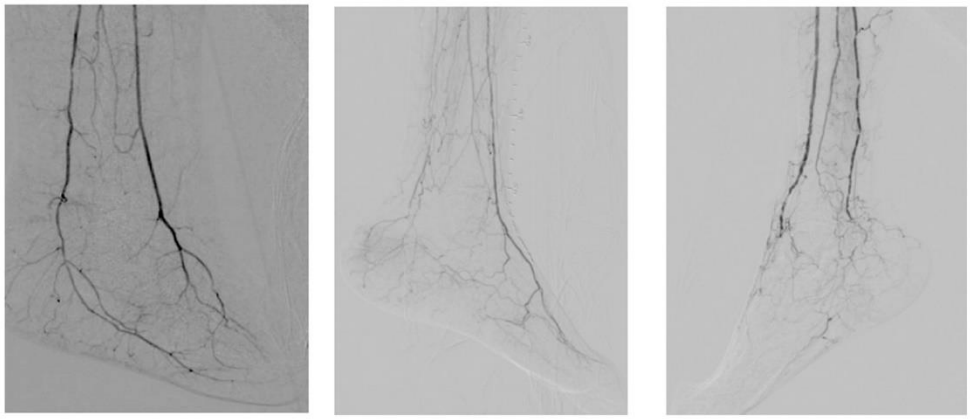
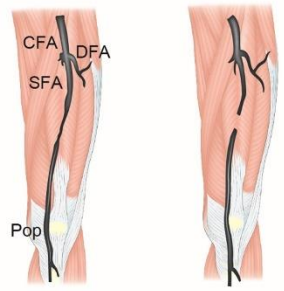
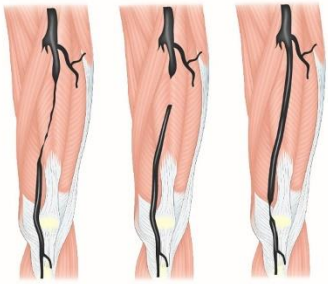
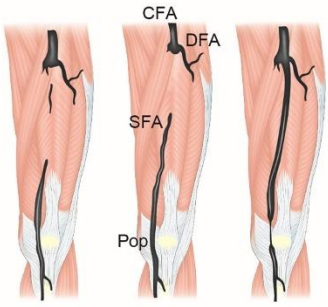
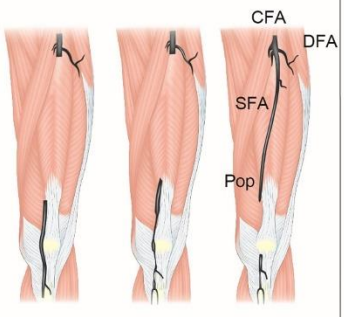


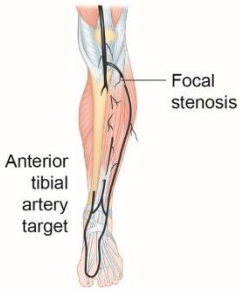
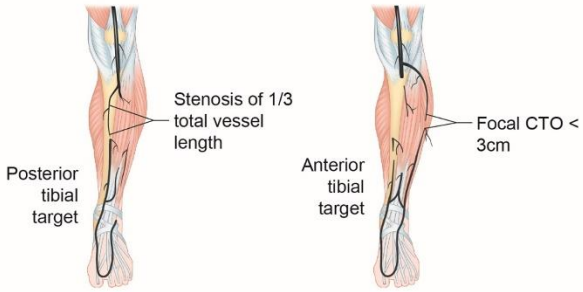
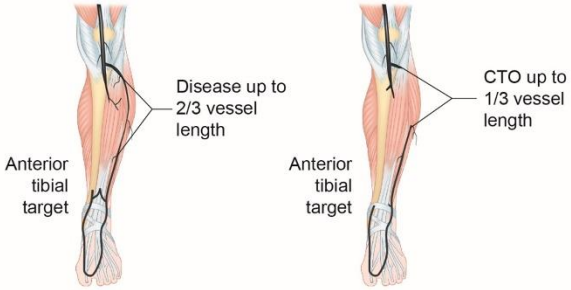
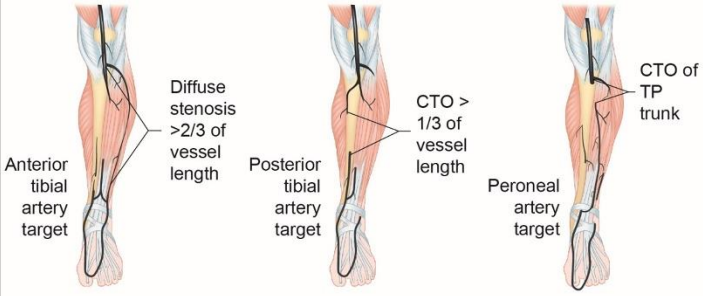
Figure 5.1. Infra-malleolar/pedal disease descriptor in GLASS. Representative angiograms of P0 (left), P1 (middle) and P2 (right) patterns of disease.

Figure 5.2 Femoropopliteal disease grading in GLASS[1]

0	Mild or no significant (<50%) disease	
1	• Total length SFA disease <1/3 (<10 cm) • May include single focal CTO (< 5 cm) as long as not flush occlusion • Popliteal artery with mild or no significant disease	
2	• Total length SFA disease 1/3-2/3 (10-20 cm) • May include CTO totaling < 1/3 (10 cm) but not flush occlusion • Focal popliteal artery stenosis <2 cm, not involving trifurcation	
3	• Total length SFA disease >2/3 (>20 cm) length • May include any flush occlusion <20 cm or non-flush CTO 10-20 cm long • Short popliteal stenosis 2-5 cm, not involving trifurcation	
4	• Total length SFA occlusion > 20 cm • Popliteal disease >5 cm or extending into trifurcation • Any popliteal CTO	

[1] Trifurcation is defined as the termination of the popliteal artery at the confluence of the AT and TP trunk

Figure 5.3 Infrapopliteal disease grading in GLASS

0	• Mild or no significant disease in the primary target artery path	
1	• Focal stenosis of tibial artery < 3cm	
2	• Stenosis involving 1/3 total vessel length • May include focal CTO (<3 cm) • Not including TP trunk or tibial vessel origin	
3	• Disease up to 2/3 vessel length • CTO up to 1/3 length (may include tibial vessel origin but not tibioperoneal trunk)	
4	• Diffuse stenosis > 2/3 total vessel length • CTO > 1/3 vessel length (may include vessel origin) • Any CTO of tibioperoneal trunk if AT is not the target artery	

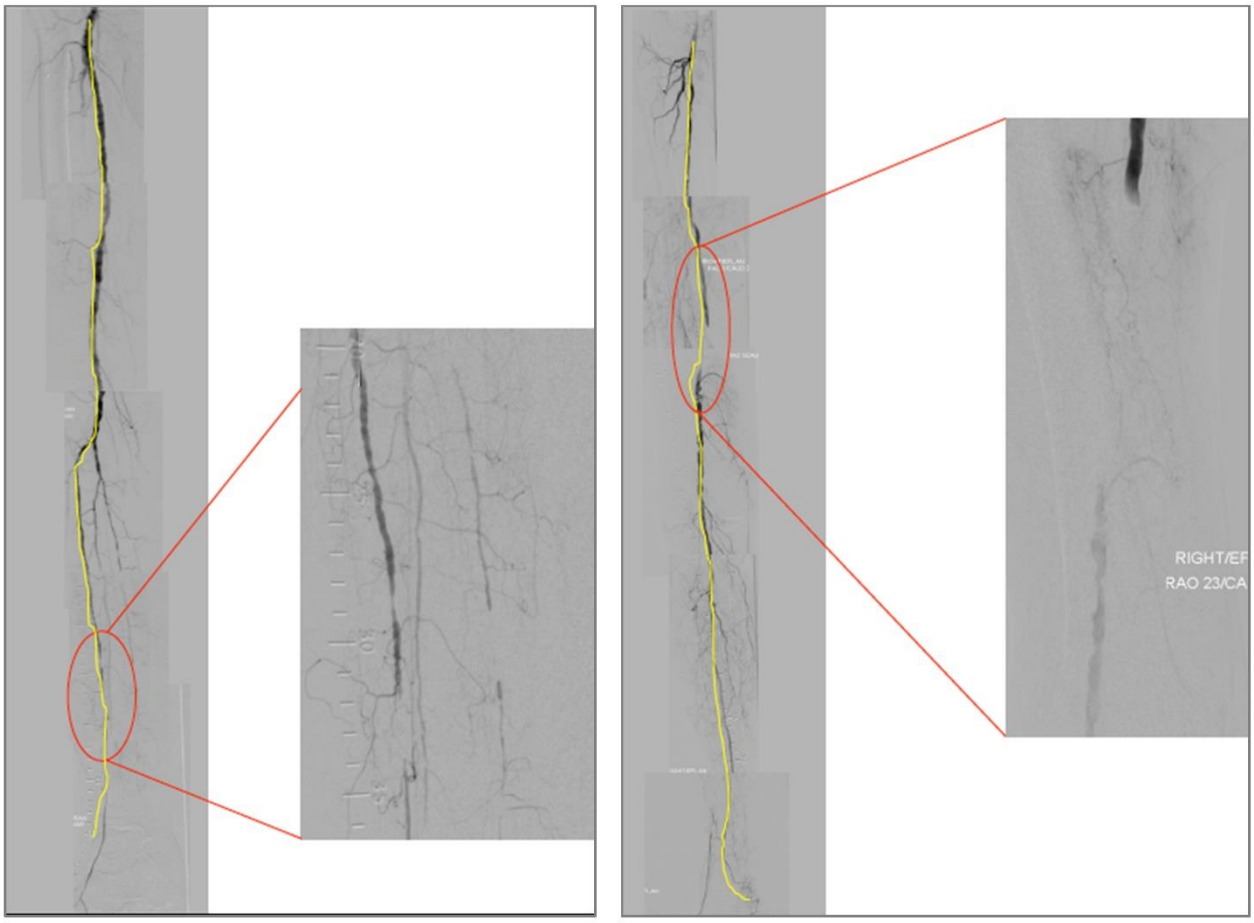


Figure 5.4 Representative angiograms of GLASS Stage 1 disease patterns. The Target Artery Path (TAP) is outlined in yellow.
Left panel. TAP includes the AT artery. FP grade is 0. IP grade is 2 (3 cm chronic total occlusion (chronic total occlusion of anterior tibial artery and total length of disease < 10 cm).
Right panel. TAP includes the peroneal artery. FP grade is 2 (chronic total occlusion < 10 cm, total length of disease < 2/3). IP grade is 0.

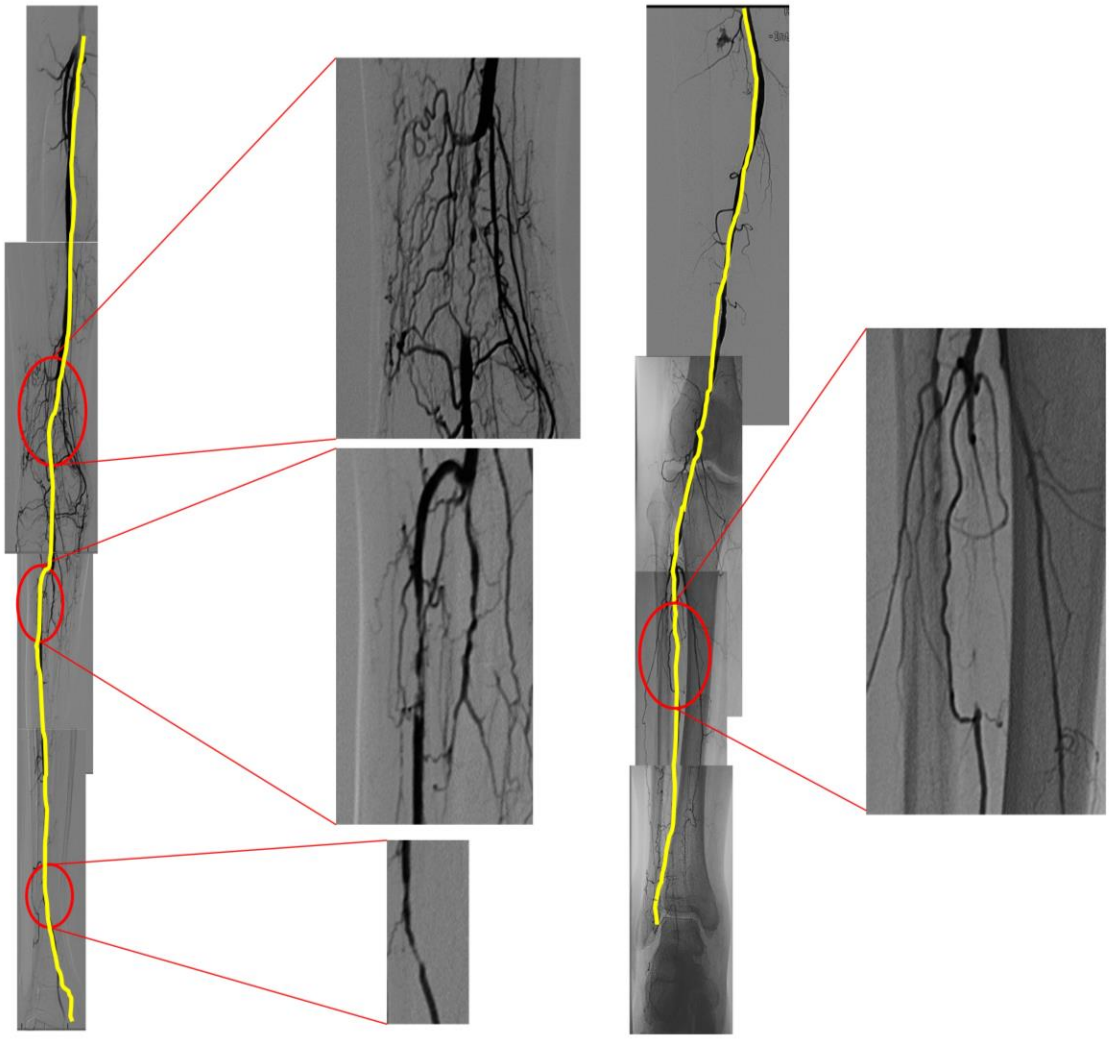


Figure 5.5. Representative angiograms of GLASS Stage 2 disease patterns. The Target Artery Path (TAP) is outlined in yellow.

Left panel. TAP includes the AT artery. FP grade is 1 (SFA occlusion < 5 cm). IP grade is 2 (two focal stenoses of anterior tiblial artery total length < 10 cm).

Right panel. TAP includes the peroneal artery. FP grade is 0 (no significant stenosis). IP grade is 3 (chronic total occlusion of peroneal artery 3-10 cm).

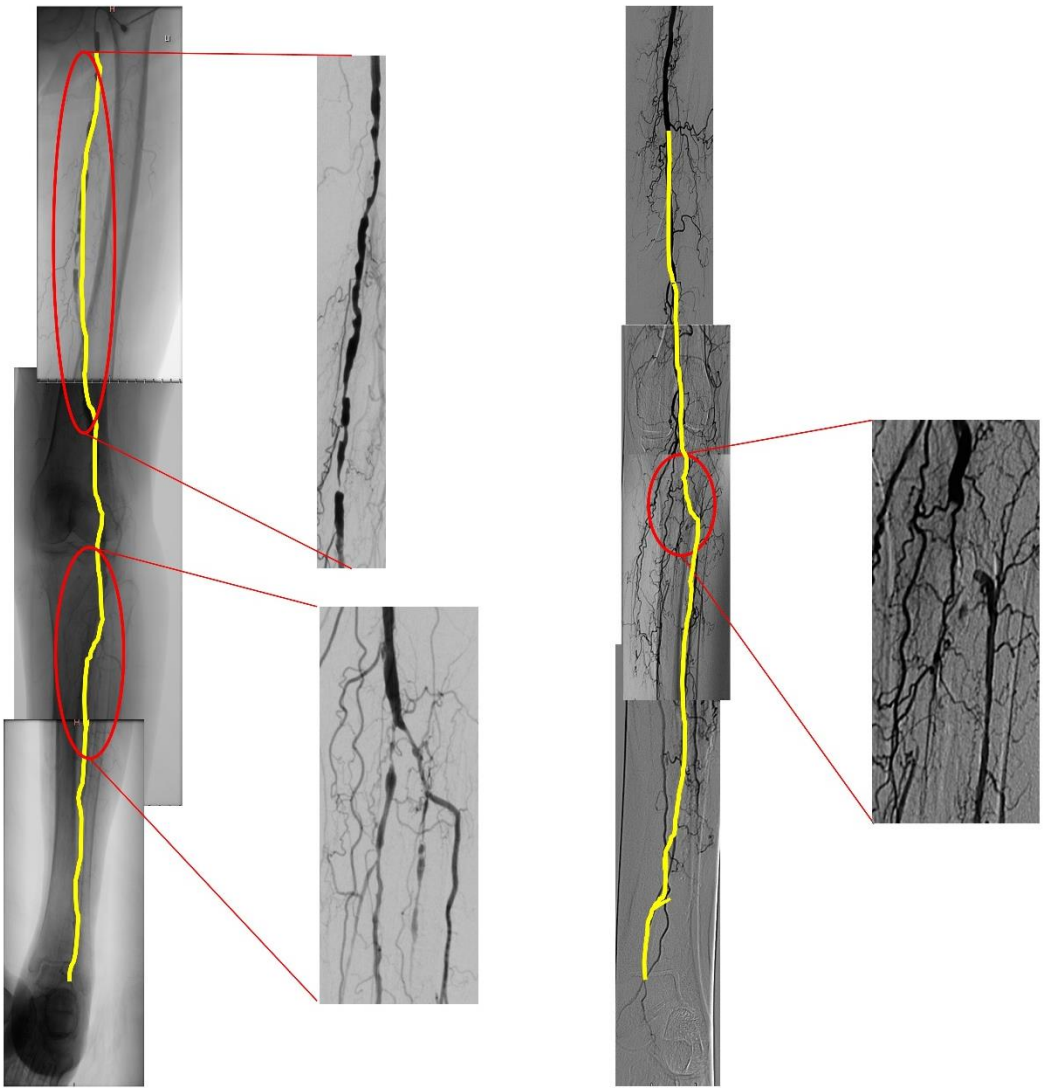


Figure 5.6. Representative angiograms of GLASS Stage 3 disease patterns. The Target Artery Path (TAP) is outlined in yellow.

Left panel. TAP includes the peroneal artery. FP grade is 4 (SFA disease length 10-20 cm, popliteal stenosis < 5 cm, heavily calcified). IP grade is 2 (stenosis of TP trunk and proximal peroneal < 10 cm).

Right panel. TAP includes the AT artery. FP grade is 4 (popliteal chronic total occlusion extending into trifurcation). IP grade is 3 (chronic total occlusion of target artery origin).

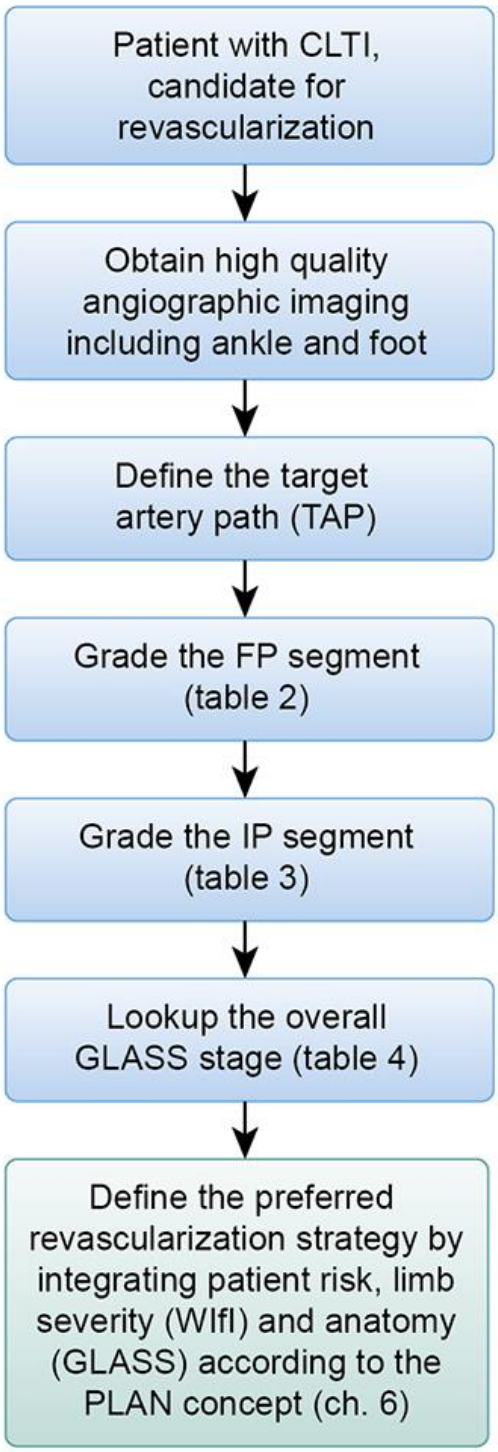


Figure 5.7 Flowchart illustrating application of GLASS to stage infrainguinal disease pattern in CLTI.

TABLE 6.1: Comparison of risk stratification tools for the CLTI population

Tool	Endpoints	Critical factors	Reference
Taylor et al	Mortality, ambulatory failure (median follow up 2 years)	Age, race, ESRD, CAD, COPD, DM, dementia, baseline ambulatory status	Taylor 2006 [405]
FINNVASC	Peri-operative (30 day) mortality, limb loss	DM, CAD, gangrene, urgent operation	Biancari 2007 [63]
PREVENT III	AFS (1 year)	ESRD, tissue loss, age > 75, CAD, anemia	Schanzer 2008 [64]
BASIL	Survival (2 years)	Age, CAD, smoking, tissue loss, BMI, Bollinger score, serum creatinine, ankle pressure (number measured and highest value), prior stroke/TIA	Bradbury 2010 [65]
CRAB	Peri-operative (30 day) mortality, morbidity	Age > 75, prior amputation/revascularization, tissue loss, ESRD, recent MI/angina, emergency operation, functional dependence	Meltzer 2013 [66]
Soga et al	Survival (2 years)	Age, BMI, non-ambulatory status, ESRD, cerebrovascular disease, tissue loss, left ventricular ejection fraction	Soga 2014 [225]
VQI	AFS (1 year)	Age, tissue loss, DM, CHF, serum creatinine, ambulatory status, urgent operation, weight, bypass conduit used	Simons 2016 [67]
VQI	Survival (30 day, 2 and 5 years)	Age, CKD, ambulatory status, CAD, CHF, COPD, tissue loss, diabetes, smoking, beta-blocker use	Simons 2018[408]

ESRD, end-stage renal disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; AFS, amputation-free survival; BMI, body mass index; TIA, transient ischemic attack; MI, myocardial infarction; CHF, congestive heart failure

FIGURES

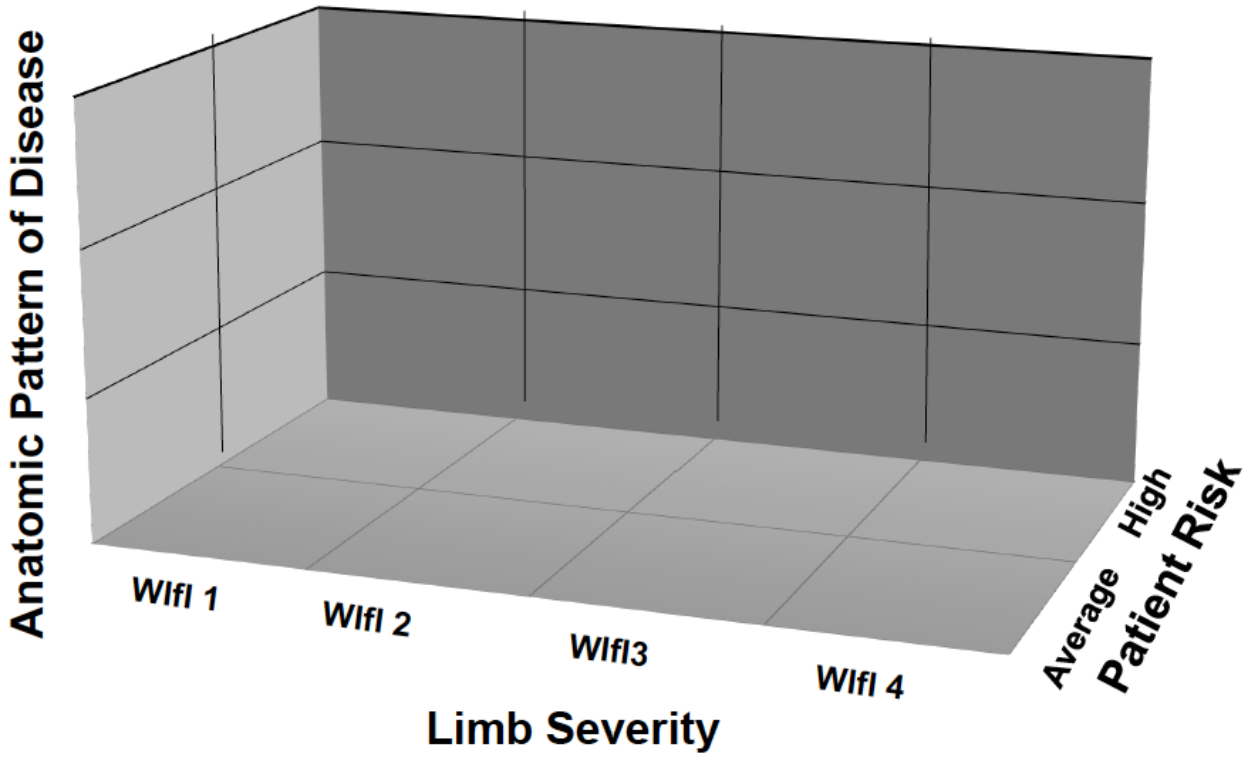


Figure 6.1. Paradigm for EBR in the treatment of CLTI. Patient risk, Limb severity, and ANatomic stage are integrated in the PLAN approach

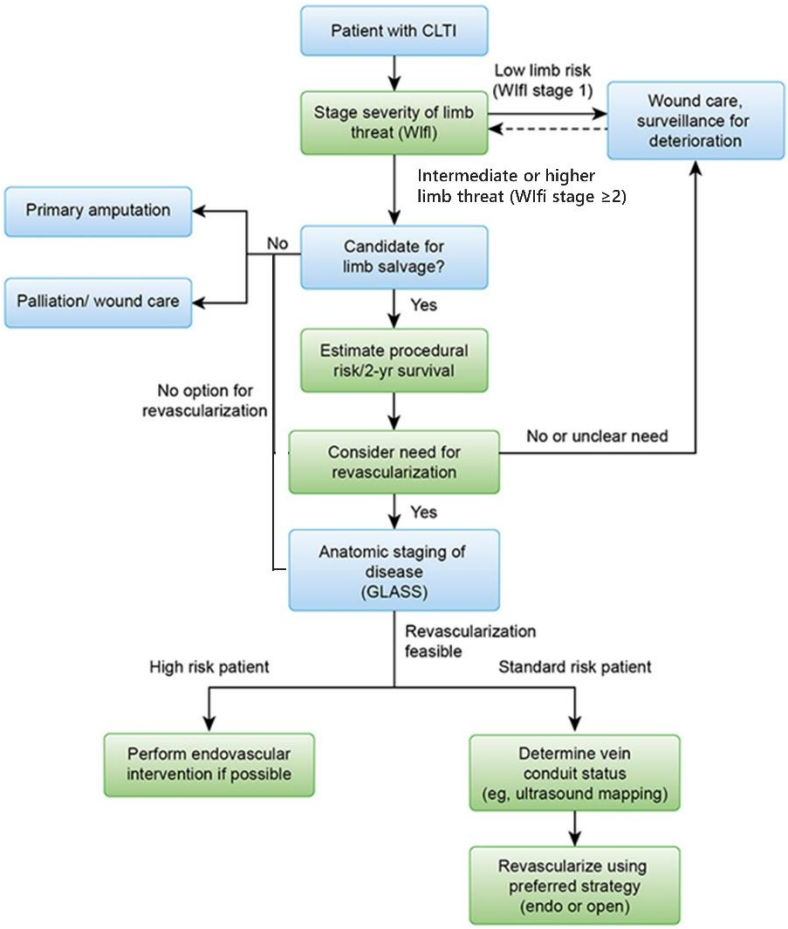


Figure 6.2. PLAN framework of clinical decision-making in CLTI; infrainguinal disease. Refer to Figure 6.4 for preferred revascularization strategy in standard risk patients with available vein conduit, based on limb stage at presentation and anatomic complexity. Approaches for patients lacking suitable vein are reviewed in text.

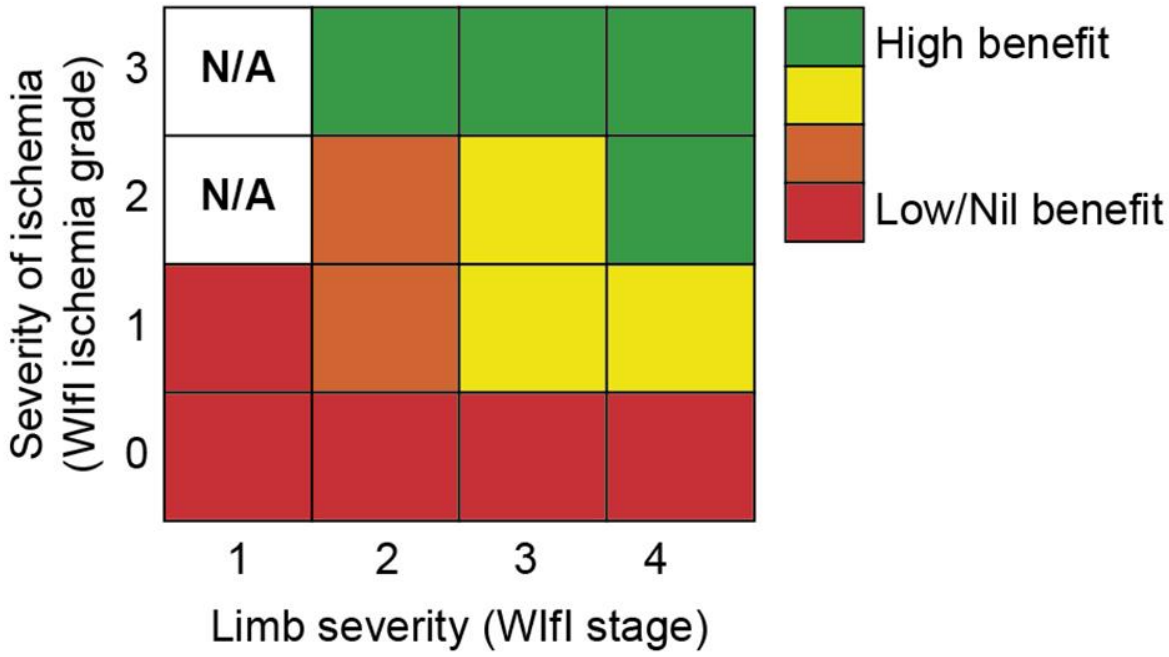


Figure 6.3. The benefit of performing revascularization in CLTI increases with degree of ischemia, and with the severity of limb threat (WIfI Stage). WIfI Stage 1 limbs do not have advanced ischemia grades, denoted as N/A.

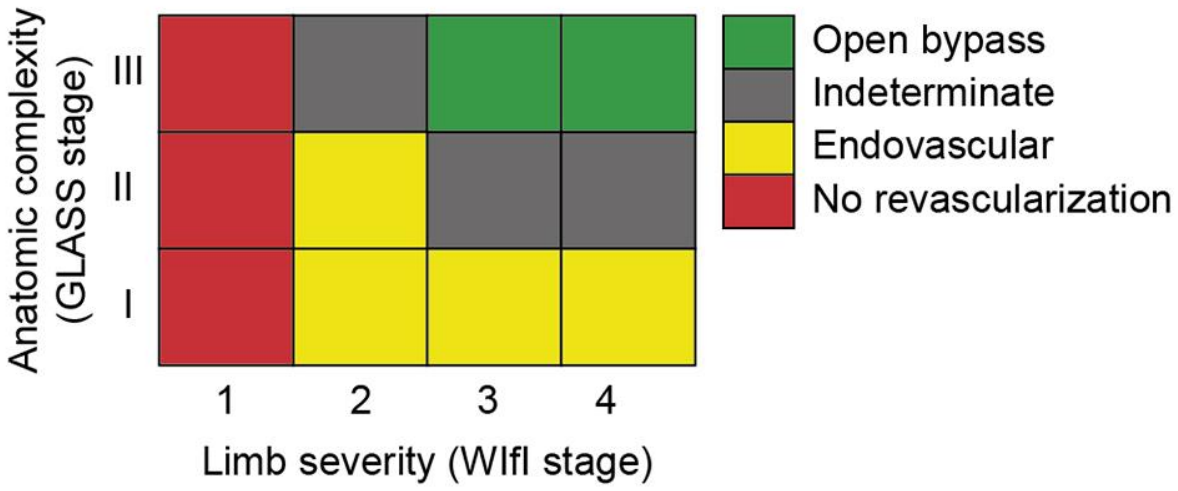


Figure 6.4. Preferred initial revascularization strategy for infrainguinal disease, in average-risk patients with suitable autologous vein conduit available for bypass. Revascularization is considered rarely indicated in low limb-risk settings (WIfI Stage 1).
Anatomic stage (*y*-axis) as determined by GLASS; limb risk (*x*-axis) as determined by WIfI staging. Dark grey shading indicates scenarios with least consensus. (Assumptions- inflow disease either not significant or is corrected; absence of severe pedal disease ie, no GLASS P2 modifier).

Table 8.1. Major trials of gene therapy and cell therapy

Trial	Treatment	Number of participants	Endpoints			Reference
			AFS at 12 months (treated vs placebo)	Other endpoints	Treatment vs placebo	
Gene Therapy						
TALISMAN	FGF	125	73% vs 48% (P = 0.009)			Nikol et al 2008[518]
Tamaris	FGF	525	63% vs 67% (P = 0.48)			Belch et al 2011[520]
HGF-STAT	HGF	104	No difference	Change in $TcPO_2$ at 6 months	25.2 mm Hg in high dose group vs 9.4 mm Hg in placebo group (P = 0.0015)	Powell et al 2008 [522]
HGF-0205	HGF	27	No difference	Change in TBI at 6 months	+0.05 vs -0.17 (P = 0.047)	Powell et al 2010 [521]
Shigematsu et al	HGF	40	No difference	Improvement in rest pain or reduction in ulcer size	70.4% vs 30.8% (P = 0.014)	Shigematsu et al 2010[523]
Cell Therapy						
Iafrati et al	Autologous bone marrow	97	No difference	Improvement in pain at 6 months Improvement in TBI at 6 months	58% vs 26% (P = 0.025) 0.48 vs 0.012 (P = 0.02)	Iafrati et al 2011, 2016[524,526]
RESTORE-CLI	Expanded autologous stem cells	72	No difference	Combined outcomes (1 year freedom from major amputation, mortality, increased wound size, new gangrene)	40% vs 67% (P = 0.045)	Powell et al 2012[528]
MOBILE	Autologous bone marrow cells	152	80% vs 69% (P = not significant)			Murphy et al 2011, 2016[524,527]
JUVENTUS	BMMNC	160	77% vs 84% (at 6 months) No difference	Major amputation at 6 months	19% vs 13% (P = not significant)	Teraa 2015[531]

Table 9.1. Major Amputation of the Lower Extremity

Level of Amputation	Below Knee	Through Knee	Above Knee
Primary Healing	30% - 92%	60% - 81%	60% - 95%
Peri-Operative Mortality	4% - 10%	1%-17%	10% - 20%
Revision to Higher Level	12% - 20%	1.5% - 20%	8% - 12%
Ambulation	40% - 80%	57% - 70%	20% - 40%

Table 11.1. IDEAL: stages of surgical and endovascular innovation for CLTI

Stage	1 Idea	2a Development	2b Exploration	3 Assessment	4 Long term study
Patients	Single digit, highly selected and homogeneous	Few; selected and homogeneous	Many; more heterogeneous	Many; expanded but well defined indications	All eligible
Vascular specialists	Very few; innovators	Few; innovators and early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement and some comparison	Comparison	Regional and international variance; quality assurance; risk stratification and adjustment
Procedure	Inception	Development	Refinement	Fully evolved	Fully evolved
Method	Structured case report	Prospective development study	Prospective cohort study; feasibility / explanatory RCT	RCT	Registries and databases
Outcomes	Proof of concept; technical achievement; disasters; notable successes	Technical success; emphasis on safety and reproducibility	Safety; objective clinical and patient reported outcomes	Objective clinical and patient reported outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Yes, usually	Yes, always	Yes, always	Yes, always	Yes, always

Table 11.2. BASIL 2/3 and BEST-CLI trial endpoints

Endpoints	BASIL 2/3	BEST-CLI
Primary	**AFS**	**MALE-Free Survival**
Secondary	Freedom from all-cause mortality In-hospital and 30-day morbidity and mortality MALE MACE Relief of ischemic pain Psychological morbidity HRQL: generic and disease-specific instruments Re- and cross-over intervention rates Healing of tissue loss (ulcers, gangrene) Extent and healing of minor amputations Hemodynamic changes; absolute ankle and toe pressures, ABI, TBPI HRQL (VascuQoL and EQ-5D) Health economic analysis	Freedom from all-cause mortality RAFS Freedom from MALE + POD AFS Freedom from myocardial infarction (MI) Freedom from stroke Freedom from reinterventions (major and minor) in index leg Number of reinterventions (major and minor) per limb salvaged Freedom from hemodynamic failure Freedom from clinical failure Freedom from CLTI HRQL (VascuQoL and EQ-5D) Health economic analysis

Abbreviations: MALE, major adverse limb event; MACE, major adverse cardiac event; HRQL, health-related quality of life; VascuQoL, vascular quality of life; ABI, ankle-brachial index; TBPI, toe-brachial pressure index; EQ-5D, EuroQol five dimensions questionnaire; RAFS, reintervention and amputation-free survival; POD, peri-operative death.

Table 12.1. The three tiers of care for amputation prevention/diabetic foot care centers

Clinical Level of Care	Setting	Potential Clinicians	Role
Basic Model of Care	General practitioner's office, health center, small community hospital	General practitioner Internist Endocrinologist Podiatrist Diabetic nurse Physical therapist	Close collaboration with a referral center
Intermediate Model of Care	Regional hospital or multidisciplinary clinic	Endocrinologist Vascular surgeon Interventionalist Orthopedic surgeon Podiatric surgeon Diabetic nurse Wound nurse Physical therapist Diabetes educator Nutritionist	Active collaboration with other departments in the hospital and extramural facilities
Center of Excellence	Large teaching hospital, tertiary referral center	Endocrinologist Vascular surgeon Interventionalist Podiatric surgeon Orthopedic surgeon Infectious disease specialist Orthotist Diabetes educator Nutritionist Wound nurse Physical therapist	Collects and reports outcomes, facilitates regional education

Adapted from Rogers LC, et al.[646]

Table 12.2. Criteria for Center of Excellence designation in CLTI or amputation prevention

Center of Excellence Criteria	Description
Multidisciplinary team of specialists	Specialists who can surgically and medically manage PAD and infections and provide the general or intensive medical care needed for the complex CLTI patient.
Protocol-driven care	A team that follows written, evidence-based clinical practice pathways, policies, and procedures.
Outcomes monitoring and reporting	Established a process for data collection and reports that data to the community or in the literature
Methods of improvement	Establishes a process for continual improvement based on outcomes and new techniques or therapies
Educational resource	Serves as an educational resource for the medical community via mentoring, publishing, and symposia

Table 12.3. The eight essential skills to prevent amputations in diabetes and the possible specialty responsible.

Essential Skills	Possible Team Members
The ability to perform hemodynamic and anatomic vascular assessment.	Vascular surgeon Interventionalist (cardiologist or radiologist) Vascular medicine
The ability to perform a peripheral neurologic workup	Neurologist Endocrinologist Podiatrist
The ability to perform site-appropriate culture technique	Infectious disease Surgeon Wound nurse Physical therapist
The ability to perform wound assessment and staging/grading of infection and ischemia	Vascular surgeon Podiatrist Surgeon Infectious disease Wound nurse Physical therapist
The ability to perform site-specific bedside and intraoperative incision and drainage or debridement	Podiatric surgeon Orthopedic surgeon Plastic surgeon Surgeon Vascular surgeon
The ability to initiate and modify culture-specific and patient-appropriate antibiotic therapy	Infectious disease Endocrinologist Primary care physician Vascular surgeon Podiatrist Surgeon
The ability to perform revascularization	Vascular surgeon Interventionalist (cardiologist or radiologist)
The ability to perform soft tissue or osseous reconstruction of deformities and defects	Podiatric surgeon Plastic surgeon Orthopedic surgeon Surgeon
The ability to perform appropriate postoperative monitoring to reduce risks of reulceration and infection	Podiatrist Wound nurse

Adapted from Fitzgerald RH, et al.[607]

Table 12.4. Major outcome measures for CLTI and Amputation Prevention

Quality Assurance Measure	Calculation
Limb salvage rate	#of total Patients - # of major amputations (BKA or AKA) / # of total patients
Major to minor amputation ratio	#of major amputations performed (BKA or AKA) / #of limb-sparing amputations performed
Healing percent – all wounds	# of wounds healed / total # of wounds – palliative care patients
Healing percent – DFUs	# of DFUs healed / total # of DFUs – palliative care patients
Median days to heal – all wounds	Calculate days to heal for all wounds. Exclude amputated and palliative patients.
Median days to heal – DFUs	Calculate days to heal for all DFUs. Exclude amputated and palliative patients.
Non-invasive vascular study – DFUs	# of NIVS performed / # of new DFU patients
Revascularization success – open bypass	# of open bypass patients - # open bypass failures / # of open bypass patients
Revascularization success - endovascular	# of endovascular patients - # endovascular failures / # of endovascular patients

AKA = above-knee amputation, BKA = below-knee amputation, DFU = diabetic foot ulcer, NIVS = non-invasive vascular study. Palliative patients are defined as those in which healing is not the treatment goal, ie, terminal or hospice patients.

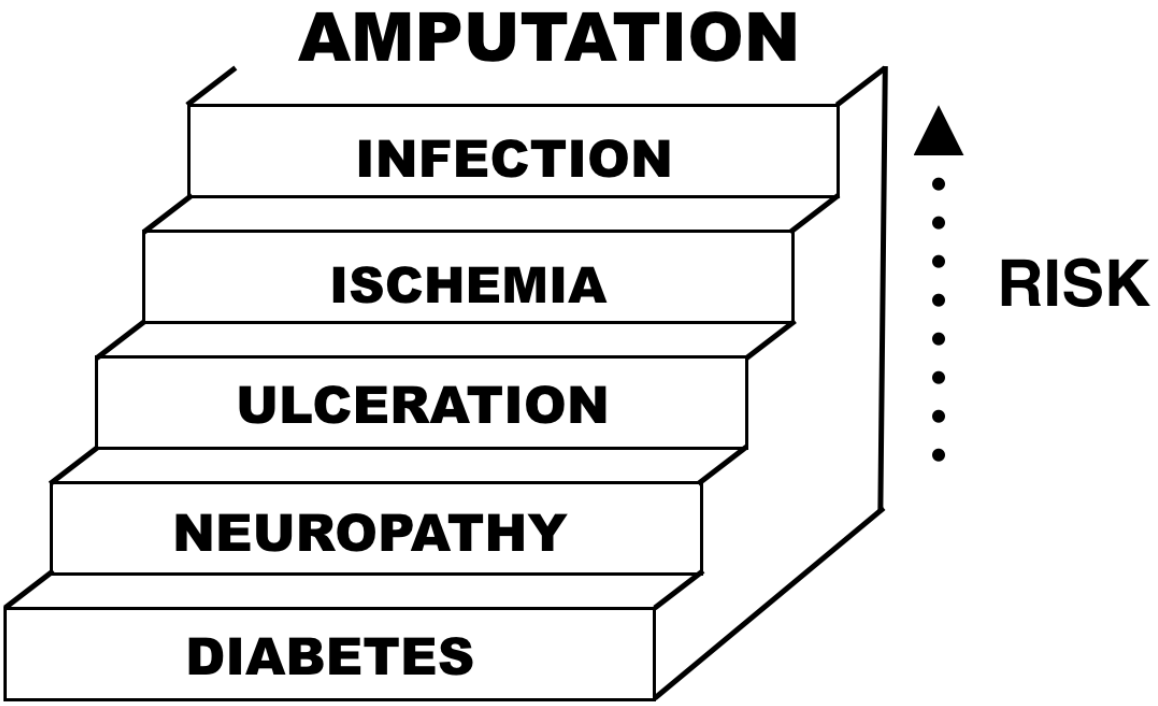


Figure 12.1. The elevating risk of the "Stairway to an Amputation," or the natural history of diabetes-related amputations. Adapted from Rogers LC and Armstrong DG. "Podiatry Care," in Cronenwett and Johnston *Rutherford's Vascular Surgery*, 7th Ed., Elsevier, 1747-1760, 2010.[647]

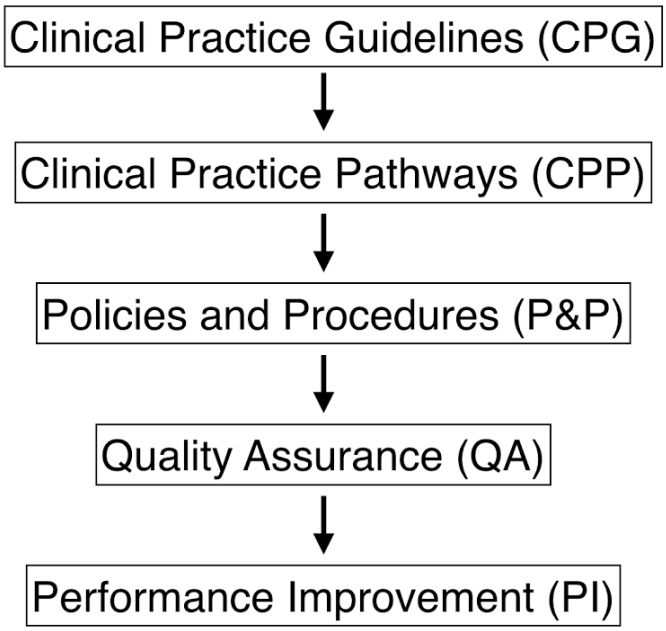


Figure 12.2. A schematic on how to organize the diabetic foot care within a multidisciplinary team.

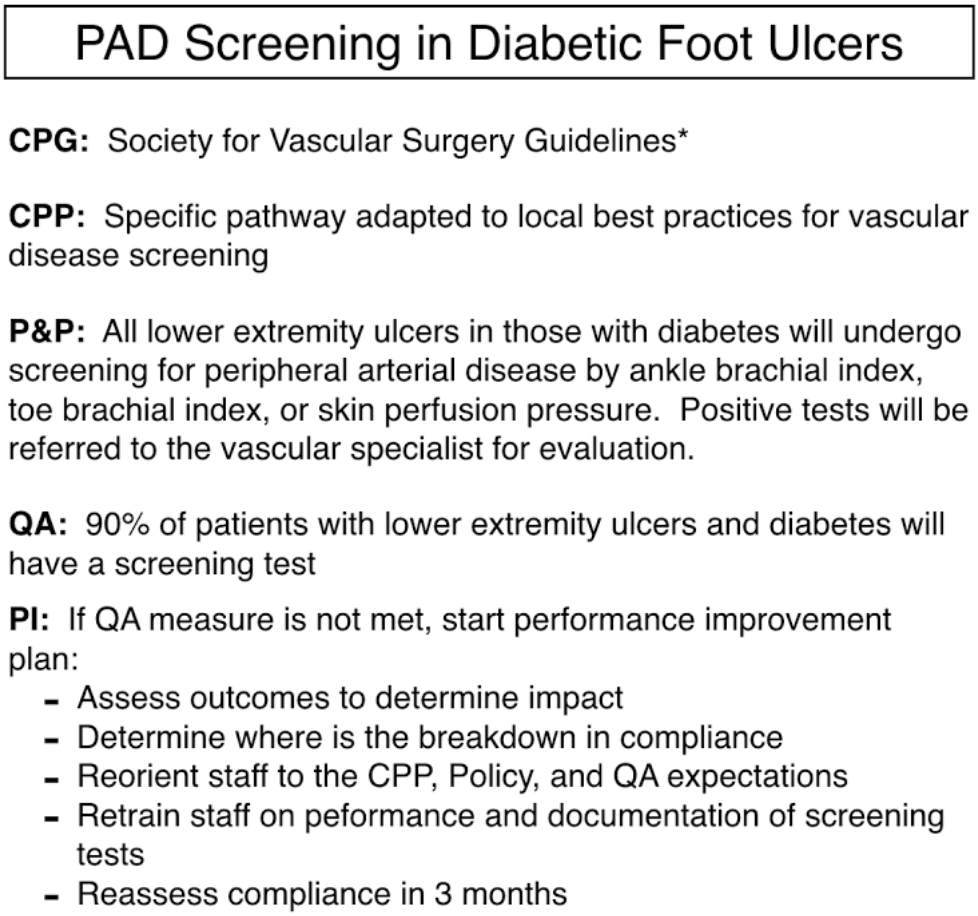


Figure 12.3. An example of using the organized care model for PAD Screening in DFUs

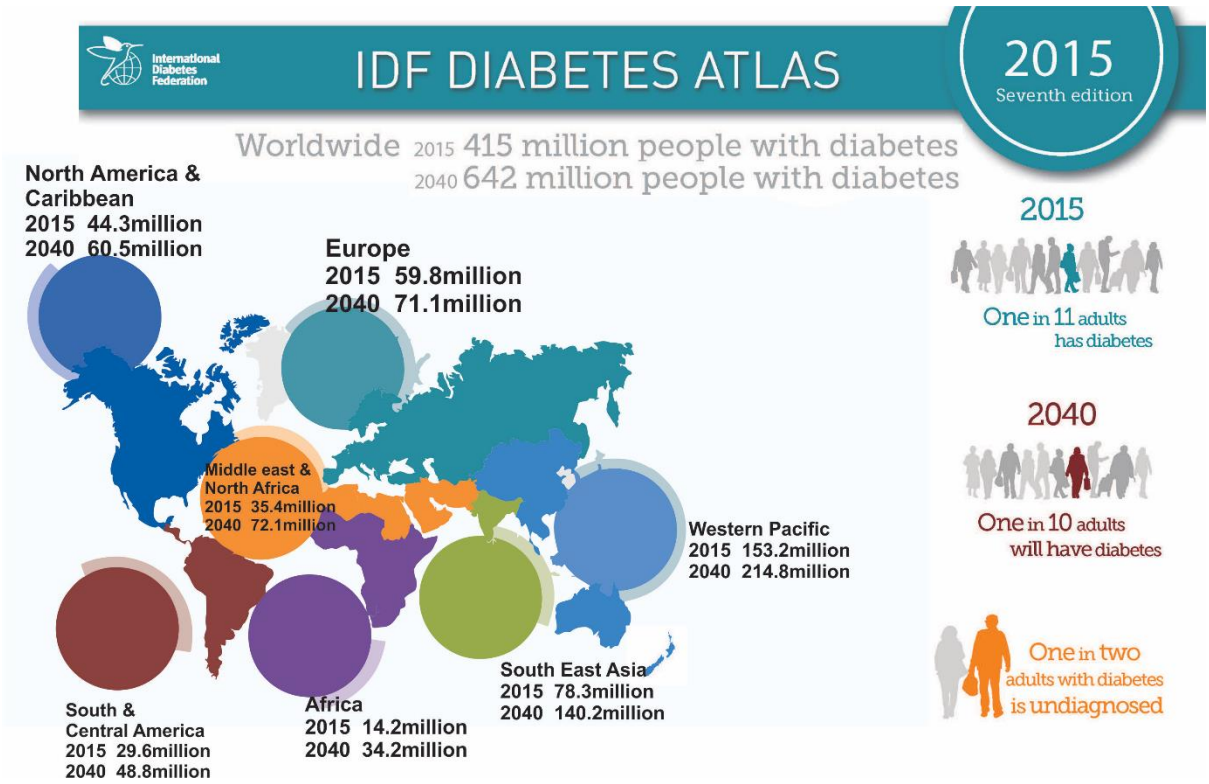


Figure 13.1: International Diabetes Foundation Global Diabetes Projections

	Rate of change (%), 2000-10		
	High-income countries	**Low-income and middle-income countries**	**Worldwide**
25-29 years	3.02	11.91	10.34
30-34 years	-1.52	7.62	5.82
35-39 years	-4.12	22.49	16.19
40-44 years	-3.28	32.05	22.59
45-49 years	7.14	25.83	20.51
50-54 years	12.15	42.40	32.37
55-59 years	31.31	55.53	47.49
60-64 years	16.85	29.90	25.06
65-69 years	4.90	20.29	14.35
70-74 years	8.02	29.73	20.05
75-79 years	11.68	41.36	26.75
80-84 years	51.98	45.77	48.92
85-89 years	34.80	47.86	39.84
≥90 years	37.22	58.82	44.09
Total	13.08	28.67	23.51

Table 13.1. Estimated number of people living with peripheral artery disease. Adapted from: Fowkes et al. 2013[11]

Country/Year	**1990 - 2000**	**2000 -2010**	**2010 +**
Benin	NA	NA	42
Ethiopia	11.6	NA	NA
Ivory Coast	NA	NA	22%
Malawi	15	NA	NA
Nigeria	NA	54	52
South Africa	10.2	8.2	30
Sudan	10	NA	NA
Tanzania	12..5	21	26
Uganda	NA	NA	39
Zambia	NA	NA	41

Table 13.2: Prevalence of PAD (%) in Diabetics. Adapted from manuscript Abbas ZG, Archibald LK. *Recent International Development: Africa*. Chapter 34, The Foot in Diabetes. Edited by: Boulton AJM, Cavanagh P, Rayman G. 4thEdition, John Wiley & Sons Ltd, www.wiley.com ;2006;379-385). Updated by Dr. Abbas Z.G (Tanzania) with review of regional data and literature. [38]

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NOTE: All the respondents are vascular surgeons

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